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Proposed Re-evaluation Decision

Formetanate Hydrochloride

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Overview

Proposed Re-evaluation Decision for Formetanate Hydrochloride

After a re-evaluation of the insecticide formetanate hydrochloride, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing continued registration of products containing formetanate hydrochloride for sale and use in Canada.

An evaluation of available scientific information found that under the revised conditions of use, products containing formetanate hydrochloride have value in the food and crop industry and do not present unacceptable risks to human health or the environment. As a condition of the continued registration of formetanate hydrochloride, new risk-reduction measures are proposed for inclusion on the labels of all products. Additional data are being requested.

The PMRA's pesticide re-evaluation program considers potential risks as well as the value of pesticide products to ensure they meet modern standards established to protect human health and the environment. Regulatory Directive DIR2001-03, the PMRA Re-evaluation Program, presents the details of the re-evaluation activities and program structure. Re-evaluation draws on data from registrants, published scientific reports, information from other regulatory agencies and any other relevant information available.

This proposal affects all end-use products containing formetanate hydrochloride registered in Canada. Once the final re-evaluation decision is made, registrants will be instructed on how to address the new risk-reduction measures.

This Proposed Re-evaluation Decision is a consultation document[1] that summarizes the science evaluation for formetanate hydrochloride and presents the reasons for the proposed re-evaluation decision. It also proposes additional risk-reduction measures to further protect human health and the environment.

The information is presented in two parts. The Overview describes the regulatory process and key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessment of formetanate hydrochloride.

The PMRA will accept written comments on this proposal up to 60 days from the date of publication of this document. Please forward all comments to Publications (please see contact information on the cover page of this document).

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1 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

What Does Health Canada Consider When Making a Re-evaluation Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions or proposed conditions of registration.[2] The Act also requires that products have value[3] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies hazard and risk assessment methods as well as policies that are rigorous and modern. These methods consider the unique characteristics of sensitive populations in humans (e.g. children) and organisms in the environment (e.g. those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the PMRA's website at www.pmra-arla.gc.ca.

Before making a re-evaluation decision on formetanate hydrochloride, the PMRA will consider all comments received from the public in response to this consultation document.[4] The PMRA will then publish a Re-evaluation Decision[5] for formetanate hydrochloride, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Formetanate Hydrochloride?

Formetanate hydrochloride is a broad spectrum, Resistance Management Group 1A (carbamate) insecticide that acts as a cholinesterase inhibitor. It works by contact and stomach (ingestion) action. Formetanate hydrochloride is registered in Canada for use on apples, pears, peaches and nectarines to control white apple leafhopper (apples only), European red mites and twospotted spider mites. Aerial application of this active ingredient is not supported by the registrant.

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2 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

3 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact".

4 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

5 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Health Considerations

Can Approved Uses of Formetanate Hydrochloride Affect Human Health?

Additional risk-reduction measures are required on formetanate hydrochloride labels. Formetanate hydrochloride is unlikely to affect your health when used according to the revised label directions.

People could be exposed to formetanate hydrochloride by consuming food and water, when working as a mixer/loader/applicator or by entering treated sites. The PMRA considers two key factors when assessing health risks: the dose levels at which no health effects occur and the dose levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g. children and nursing mothers). Only those uses where exposure is well below levels that cause no effects in animal testing are considered acceptable for continued registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when using formetanate hydrochloride products according to label directions.

Acute overexposure to formetanate hydrochloride can inhibit cholinesterase, an enzyme necessary for normal functioning of the nervous system. This can produce a variety of symptoms in animals and humans including tremors, body stiffening, lacrimation, salivation, convulsions, unsteady gait, vomiting, laboured respiration, decreased motor activity, lethargy and muscle weakness. With formetanate hydrochloride, cholinesterase inhibition can occur rather rapidly with exposure (within minutes), but rapidly recovers along with any of the aforementioned symptoms. Young animals in toxicity studies were more sensitive than the adults following oral exposures, with more pronounced effects on cholinesterase observed. Inhaling formetanate hydrochloride resulted in low to moderate acute toxicity, depending on the duration of dosing. Local effects of acute dermal exposure were minimal; however, the potential for skin sensitization does exist. Contact with the eye may also cause moderate eye irritation. To prevent overexposure, the label directions must be followed.

Additional findings in repeat-dose animal studies including those in pregnant animals consisted of decreases in body-weight gain and food consumption. There were a small number of positive genotoxicity results noted, however, the findings were equivocal at best; overall there was no great concern with respect to genotoxicity with most studies showing negative results. Likewise, while higher dose levels could have been employed in certain cancer studies, there was no concern identified with respect to carcinogenicity. A cancer risk assessment was not required. The described effects would likely not occur when formetanate hydrochloride products are used according to the label directions.

As there were some risks of concern based on current uses of formetanate hydrochloride, additional protective measures have been proposed for inclusion on product labels to further reduce the level of human exposure to formetanate hydrochloride.

Risks in Residential and Other Non-Occupational Environments

Non-occupational risks are not of concern.

There are currently no residential uses of formetanate hydrochloride registered. Given homeowners would not be applying the product, a risk assessment for this scenario was not conducted.

Occupational Risks From Handling Formetanate Hydrochloride

Occupational risks are not of concern provided additional risk-reduction measures are observed.

Risk estimates associated with applying, mixing and loading activities for the global label uses are acceptable, provided engineering controls and/or personal protective equipment are used. These measures are needed to minimize potential exposure and protect worker's health.

Postapplication risks are not of concern to workers provided additional risk-reduction measures are observed.

Postapplication occupational risk assessments consider exposures to workers entering treated sites in agriculture. When the proposed mitigation measures are considered, postapplication risks are not of concern.

Residues in Water and Food

Reference doses define levels to which an individual can be exposed over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and water is acceptable if it is less than 100% of the acute reference dose or chronic reference dose (acceptable daily intake). An acceptable daily intake is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects.

Human exposure to formetanate hydrochloride was estimated from residues in treated crops and drinking water, including the most highly exposed subpopulation (e.g. infants less than one year old). Two approaches were used to assess dietary risk. In the first approach, limited field trial data were used to estimate residues in food. Given there were limitations in the field trial data, a second approach was used in which monitoring data of residues in foods available to Canadian consumers were used. Using the former approach, aggregate exposure (i.e. to formetanate hydrochloride from food and drinking water) represents less than 75% of the acute reference dose and less than 2% of the

chronic reference dose. When using the latter approach, aggregate exposure is less than 96% of the acute reference dose and less than 0.3% of the chronic reference dose for all subpopulations, with the exception of infants. Aggregate exposure for infants is greater than 400% of the acute reference dose, indicating that risk mitigation for dietary exposure is required for this subpopulation.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for the *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Each MRL value defines the maximum concentration in parts per million (ppm) of a pesticide allowed in or on certain foods. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

MRLs for formetanate hydrochloride are currently specified for apples, pears, peaches, nectarines, citrus fruits and plums. Where no specific MRL has been established, a default MRL of 0.1 ppm applies, which means that pesticide residues in a food commodity must not exceed 0.1 ppm. Given changes in the use pattern of formetanate hydrochloride and as a result of the dietary risk assessment, the MRLs for formetanate hydrochloride need to be revised.

Environmental Considerations

What Happens When Formetanate Hydrochloride is Introduced Into the Environment?

Formetanate hydrochloride poses a potential risk to beneficial predatory terrestrial invertebrates and aquatic invertebrates; therefore, additional risk reduction measures need to be observed.

Formetanate hydrochloride is very soluble in water and is very susceptible to hydrolytic transformation and phototransformation in both soil and water at neutral and basic pH conditions. Acidic conditions result in slower transformation of parent formetanate hydrochloride. Soil biotransformation also takes place quickly so formetanate hydrochloride is unlikely to persist in soil or water after application. There were no major transformation products formed in any of these processes. Formetanate hydrochloride is considered to have moderate mobility in most soils; however, modelling predicts that only low concentrations will reach surface water and no residues will be found in ground water.

When formetanate hydrochloride is used for insect control in crops, there is a potential that nontarget species on land and in water may be exposed to the chemical as a result of spray drift or runoff. Some species are sensitive to the chemical and would be adversely affected. Formetanate hydrochloride presents a risk to aquatic organisms like freshwater invertebrates and terrestrial beneficial predatory insects and mites. To minimize potential exposure to these biota, strips of land between the agricultural field and the nontarget areas will be left unsprayed. The width of these buffer zones will be specified on the

product label. An appropriate label statement describing the risk to beneficial predatory terrestrial insects is required.

Birds and small mammals could be at risk from the use of formetanate hydrochloride, however, the risk assessment is considered to be overly conservative due to the fact that formetanate hydrochloride has rapid photolytic and hydrolytic transformation. These factors indicate that it is unlikely that these biota will be exposed to formetanate hydrochloride at sufficient concentrations to result in risk. Fish and marine invertebrates are at negligible risk from use of formetanate hydrochloride.

Modelling predicts that formetanate hydrochloride will not be present in runoff, or in surface waters due to drift, at concentrations that present a risk to aquatic biota.

Measures to Minimize Risk

Registered pesticide product labels include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law. As a result of the re-evaluation of formetanate hydrochloride, the PMRA is proposing further risk-reduction measures for product labels to address potential risks identified in this assessment.

Additional Key Risk-Reduction Measures

Human Health

- Limit application to once per season, reduce rate of application and limit timing of application to early season to minimize residues on treated food crops.
- Require additional protective equipment and/or engineering controls, limit application to once per season, reduce rate of application and remove aerial application to protect mixer/loader/applicators.
- Limit application to once per season, reduce rate of application, limit timing of application to early season and establish restricted-entry intervals to protect workers entering treated sites.

Environment

- Adding precautionary label statements and directions for use as well as buffer zones to protect non-target terrestrial and aquatic plants.
- Adding statements cautioning use on sites with characteristics that may enhance runoff when heavy rain is forecasted to reduce the potential runoff of formetanate hydrochloride to adjacent aquatic habitats.

What Additional Scientific Information is Being Requested?

Human Health

Given of changes in the use pattern of formetanate hydrochloride and as a result of the dietary risk assessment, the MRLs for formetanate hydrochloride must be re-evaluated and revised.

- To assess and revise the MRLs of formetanate hydrochloride, all residue data including field trials submitted to the United States Environmental Protection Agency (USEPA) must be submitted within one year of the final re-evaluation decision document. This includes, but is not limited to, all field trials in stone fruit, pome fruit, citrus fruit; plant and livestock metabolism studies; food processing studies; analytical methodology studies; and storage stability studies. To facilitate the PMRA review, it is highly recommended that USEPA reviews of these studies be submitted also.

- In addition, all residue data including field trials to be submitted to the USEPA as a result of their evaluation as outlined in the document: *Formetanate Hydrochloride HED Revised Chemistry Chapter of the RED: Summary of Analytical Chemistry and Residue Data (Phase 4)* must be submitted within one year of the final re-evaluation decision. This includes, but is not limited to, all field trials in stone fruit, pome fruit, citrus fruit and clarifications for plant metabolism studies.

Next Steps

Before making a re-evaluation decision on formetanate hydrochloride, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will then publish a Re-evaluation Decision, which will include the decision, the reasons for it, a summary of comments received on the proposed decision and the PMRA's response to these comments.

Other Information

When the re-evaluation decision is made, the PMRA will publish an Evaluation Report on formetanate hydrochloride in the context of this re-evaluation decision (based on the Science Evaluation section of this consultation document). In addition, the test data on which the decision is based will also be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Once all carbamate pesticides have been re-evaluated, a cumulative risk assessment will be conducted, which will consider potential exposure to all chemicals causing toxicity in the same manner. The results of the cumulative risk assessment may affect any previous re-evaluation decision.

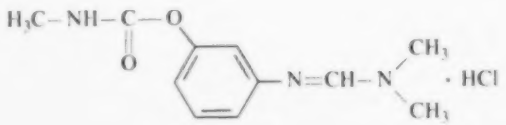
Science Evaluation

1.0 Introduction

Formetanate hydrochloride is one of the pesticides subject to re-evaluation in Canada as announced in Re-evaluation Note REV2002-06, *Re-evaluation of Selected Carbamate Pesticides*. Formetanate hydrochloride is a broad spectrum, Resistance Management Group 1A (carbamate) insecticide that acts as a cholinesterase inhibitor. It works by contact and stomach (ingestion) action.

2.0 The Active Substance, Its Properties and Uses

2.1 Identity of the Active Substance

Active substance	Formetanate Hydrochloride
Function	Insecticide
Chemical names	IUPAC: 3-dimethylaminomethyleneaminophenyl methylcarbamate hydrochloride CAS: N,N-dimethyl-N'-[3-[[(methylamino)carbonyl]oxy]phenyl]methanimidamide hydrochloride
Chemical class	Carbamate
Chemical Abstracts Service registry number	23422-53-9
Molecular formula	$C_{11}H_{16}ClN_3O_2$
Molecular weight	257.8
Structural formula	
Purity of technical grade active ingredient	92% nominal (limits: 89.25–94.75%)
Registration number	25326

Identity of impurities of human health or environmental concern	Impurities of human health or environmental concern as identified in Section 2.13.4 of DIR98-04 or any TSMP Track 1 substances as identified in Appendix II of DIR99-03 are not expected to be present in the starting materials used to manufacture the product nor are they expected to be formed during the manufacturing process.

2.2 Physical and Chemical Properties of the Active Substance

Property	Result
Vapour pressure at 25°C	0.0016 mPa*
Henry's law constant at 22°C	5.0×10^{-10} Pa m^3 mol^{-1}*
Ultraviolet (UV)/visible spectrum	λ_{max} ϵ_{max} ($l.Mol^{-1}.cm^{-1}$) 211 nm 20400 252 nm 15160
Solubility in water at 25°C	822 g/ L*
n-Octanol–water partition coefficient (K_{ow})	Log $K_{ow} \leq$ -2.7 (pH 7–9)*
Dissociation constant (pKa) at 25°C	pKa = 8.0 (for formetanate)*

* From the *e-Pesticide Manual*, 12th ed., V2.2, 2002, British Crop Protection Council.

2.3 Description of Registered Formetanate Hydrochloride Uses

Appendix I lists all formetanate hydrochloride products that are registered under the authority of the *Pest Control Products Act*. Appendix II lists all the uses for which formetanate is registered, with an indication of which uses the registrant will continue to support or will no longer support. Uses registered as a User Requested Minor Use Label Expansion (URMULE) are identified (M). All uses supported by the registrant were considered in the health and environmental risk assessments of formetanate hydrochloride. Aerial application of this active ingredient is not supported by the registrant.

3.0 Impact on Human and Animal Health

Toxicology studies in laboratory animals describe potential health effects resulting from various levels of exposure to a chemical and identify dose levels where no effects are observed. Unless there is evidence to the contrary, it is assumed that effects observed in animals are relevant to humans and that humans are more sensitive to effects of a chemical than the most sensitive animal species. The health effects noted here were observed in animals at dose levels at least 100-fold (often much higher) above levels to which humans are normally exposed through use of products containing this chemical.

3.1 Toxicological Summary

The toxicology data base is primarily based on studies from the registrant. The toxicology database confirms that formetanate hydrochloride has anti-cholinesterase activity in various species and produces toxic signs typical of the N-methyl carbamate class of chemicals. Most studies were conducted with formetanate hydrochloride (also known as Carzol SP). Acute oral toxicity studies showed little difference between technical grade formetanate and formetanate hydrochloride. The form tested in most genotoxicity studies was unknown but this was likely to have minimal impact on the consideration of the database.

When orally administered, formetanate hydrochloride is rapidly absorbed and excreted, with the liver showing the highest tissue concentrations. The bulk of excretion occurred via the urine with most urinary activity excreted as water-soluble metabolites. The primary metabolites were determined to be m-formamino-phenyl-N-methylcarbamate, m-aminophenol and m-formaminophenol. Metabolites were found to be significantly less toxic than the parent compound in acute oral lethality tests.

Formetanate hydrochloride showed high acute oral toxicity in all species tested (mouse, rat and dog). Acute toxic signs induced by formetanate hydrochloride included tremors, body stiffening, lacrimation, salivation, convulsions, lethargy and muscle weakness. Cholinesterase inhibition occurred within minutes, but rapidly recovered along with the cholinergic symptoms. Acute dermal toxicity was low in the rat and rabbit, probably reflecting the slow absorption by this route as well as the rapid reactivation of the acetylcholinesterase enzyme. Formetanate hydrochloride was of low to moderate acute toxicity to rats by the inhalation route depending on the duration of dosing. Moderate eye irritation was noted in rabbits. Formetanate hydrochloride was a dermal sensitizer.

In repeat-dose studies conducted in various species (mouse, rat and dog), the dog appeared to be the most sensitive species with respect to cholinergic symptoms. Effects in dogs included coughing, trembling, salivation, unsteady gait, vomiting, laboured respiration and plasma and erythrocyte cholinesterase inhibition. Brain cholinesterase levels began to significantly decrease with the administration of higher doses. Cholinesterase inhibition was also seen in the chronic rat study. A thickening of the muscular coat of the jejunum and pylorus of the stomach of the dog suggests some chronic inflammation that resulted in scarring of these areas. Additional repeat-dose study findings from rats and mice included a decrease in body-weight gain, food consumption and/or food conversion. The rodent studies highlight the differences between gavage and dietary dosing as animals tolerated chronic dietary dose levels that were equivalent to or even exceeded the LD_{50}s seen in acute gavage studies. Repeat-dose dietary studies in the rat indicated that an increase in the duration of dosing resulted in increased toxicity with respect to brain cholinesterase inhibition. While there was no repeat dose inhalation study in the database, the inhalation route was not a significant contributor to risk associated with this use pattern and the lack of a study does not affect the risk assessment. No pronounced gender differences were noted in the database.

In an acute neurotoxicity study, formetanate hydrochloride caused an inhibition of cholinesterase activity in all compartments (brain, whole blood and plasma) at the time of peak effect

(30–60 minutes postdosing), with clinical signs, decreased motor activity and altered neurological functioning occurring at higher doses. All effects were reversible highlighting the short-acting effects typically associated with carbamate inhibitors of acetylcholinesterase. In a subchronic neurotoxicity study, no evidence of cholinesterase inhibition was observed in rats at levels that affected body-weight gain; however, chronic dosing of the rat resulted in brain cholinesterase inhibition at levels lower than those affecting body-weight gain. No evidence of neuropathology was noted in any of the available studies.

The results for most genotoxicity studies including mitotic recombination, chromosomal effects, prokaryotic DNA repair, primary DNA damage and gene mutation assays were negative. Positive results were noted only in a mouse lymphoma assay (two other mouse lymphoma assays were negative) as well as in an in vitro chromosome analysis of human lymphocytes (only without activation). No positive findings were observed in in vivo genotoxicity assays. Following nitrosation, formetanate was mutagenic in the bacterial spot test, but negative in the in vivo mouse micronucleus test; however, the ability of formetanate to undergo nitrosation in the human gut has not been established. There was no evidence of carcinogenicity in the long-term rat and mouse studies. However, it should be noted that the mouse study was considered to be marginally adequate because a maximum tolerated dose was not well-demonstrated in both sexes.

The developmental toxicity studies in rats and rabbits showed no evidence of teratogenicity and no additional sensitivity of the fetus following in utero exposure to formetanate hydrochloride. No developmental effects were noted despite observations of maternal toxicity (clinical signs, reduced weight gain and food intake) in both species. Parental effects in a two-generation reproduction study included a decrease in maternal weight gain during first filial generation (F_1) gestation, and a reduction of erythrocyte and brain cholinesterase levels in parental generation (F_0) males only. The second filial generation (F_2) offspring showed a slight reduction in growth and survival. Reproductive toxicity was seen with a slight decrease in birth weights (F_2). The observed effects in the offspring were too marginal to determine whether a sensitivity of the young was evident.

To address the uncertainty surrounding whether or not a sensitivity existed in the young, a comparative cholinesterase assay that assessed both erythrocyte and brain cholinesterase activity was performed in rats; effects in the young were compared to those in the adult population. Toxicologically significant effects were observed at the lowest dose tested in both populations with quantitative sensitivity demonstrated in the young population. As a result of the effects at the lowest dose tested, benchmark dosing was performed to refine the assessment. The benchmark responses used to estimate a dose corresponding to critical effects at each endpoint were 10% percent for brain cholinesterase inhibition and 20% for erythrocyte cholinesterase inhibition. The refined data showed a quantitative sensitivity for brain and erythrocyte cholinesterase inhibition in the young animals relative to the adults; with the young about 3 times more sensitive than the adults. As such the young animals were considered to be the most sensitive population in the database.

Reference doses have been set based on benchmark dose values ($BMDL_{10}$) or no observed adverse effect levels (NOAELs) for the most sensitive indicator of toxicity, namely

acetylcholinesterase inhibition. These reference doses incorporate various uncertainty factors to account for extrapolating between laboratory animals and humans and for variability within the human populations.

***Pest Control Products Act* Hazard Consideration**

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects. This factor should take into account completeness of the data with respect to the exposure of and toxicity to infants and children as well as potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database, extensive data were available on formetanate hydrochloride including prenatal developmental toxicity studies in rats and rabbits, four multigeneration reproduction studies (two being dose range finding studies) and a comparative cholinesterase study (examining pups and adult animals).

With respect to potential prenatal and postnatal toxicity, there was some indication of increased susceptibility in the offspring compared to parental animals in the reproduction studies; this based on slight decreases in F_2 generation pup viability and birth weights. Prenatal developmental toxicity studies provided no indication of increased susceptibility of rat or rabbit fetuses following in utero exposure to formetanate hydrochloride; however, these studies did not include measures of cholinesterase parameters. The comparative cholinesterase assay identified increased sensitivity of juveniles for cholinesterase inhibition when compared to adults. Effects on cholinesterase activity levels in the young were not assessed following in utero or lactational (i.e. "indirect" exposures) and, therefore, it is not known whether the sensitivity exists in these scenarios as well. In the absence of such information, it is assumed that these subpopulations (i.e. fetuses or nursing offspring) would demonstrate at most, a comparable degree of sensitivity to that observed in directly dosed young animals. The rapid reactivation of cholinesterase activity associated with formetanate, coupled with the placental or lactational transfer that must occur for the young to be exposed, makes it unlikely for a higher degree of sensitivity to be observed in the indirectly exposed animal compared to the directly exposed young animal. Accordingly, use of the point of departure for cholinesterase inhibition in the directly dosed young animal for risk assessment is expected to address concerns relating to indirect exposures.

Cholinesterase inhibition is the critical endpoint of concern, and the comparative cholinesterase assay shows that decreases in cholinesterase activity occur at dose levels not producing any other effects of toxicological significance. This inhibition is short-lived; hence, the potential for other neurological sequelae is limited (albeit not eliminated) due to the rapid reversibility of the test article enzyme interaction. In consideration of this information, the use of the lowest $BMDL_{10}$ for the critical endpoint of cholinesterase inhibition in the sensitive population for risk assessment addresses any residual uncertainty relating to prenatal or postnatal toxicity.

Appendix III lists the toxicology profile and endpoints used in the health risk assessment for formetanate hydrochloride.

3.2 Occupational and Non-Occupational Risk Assessment

Occupational and non-occupational risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects. However, MOEs less than the target MOE require measures to mitigate (reduce) risk. In some cases, MOEs could not be calculated for combined dermal and inhalation exposure because each route of exposure had different NOAELs and target MOEs. In these cases, an aggregate risk index (ARI) was calculated. ARIs greater than or equal to one do not require risk mitigation.

3.2.1 Toxicological Endpoints

For short-, intermediate- and long-term dermal risk assessment, the results of the single dose and the 21-day dermal toxicity studies in the rat were considered collectively for risk assessment. A NOAEL of 15 mg/kg bw/day was established based on whole blood cholinesterase inhibition at ≥20 mg/kg bw/day.

These dermal studies were conducted in adults and not in the young, where a sensitivity issue has been established via the oral route of exposure. Results from the comparative cholinesterase assay illustrated that direct exposure to oral doses of formetanate hydrochloride resulted in cholinesterase inhibition that was around threefold greater in the young than in the adults.

Uncertainty arises as to whether the fetus or nursing infant would be more sensitive than the adult. The worker population could include pregnant or lactating women, potentially resulting in indirect exposure to their offspring. Given the lack of data to assess the potential sensitivity of the fetus or nursing offspring, a threefold uncertainty factor for database deficiency is considered appropriate to protect the young. The magnitude of this factor is supported by the observation that the young are approximately threefold more sensitive than the adults after direct oral dosing to formetanate hydrochloride and the assumption that the fetus or nursing offspring is likely to be no more sensitive than the directly dosed young animal.

The target MOE is 300, accounting for standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as an extra threefold for database deficiency. The selection of this study and MOE is considered to be protective of all populations including nursing infants and the unborn children of exposed female workers.

For short-, intermediate- and long-term inhalation risk assessment, there were no repeat-dose inhalation toxicity studies that assessed cholinesterase inhibition. Thus, the acute comparative cholinesterase assay in rats was selected for risk assessment with the assumption that absorption via inhalation is equivalent to oral absorption. A $BMDL_{10}$ of 0.06 mg/kg bw/day was established based on brain cholinesterase inhibition in female pups. A target MOE of 100 is required to account for standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. This value was considered to be protective of all worker populations including women who may be pregnant or nursing.

Dermal Absorption
A dermal absorption factor is not applicable because the dermal risk assessment was based on dermal toxicity studies.

3.2.2 Occupational Exposure and Risk Assessment

Workers can be exposed to formetanate hydrochloride when mixing, loading or applying the pesticide, and when re-entering a treated site to conduct activities such as scouting and/or harvesting of treated crops.

The occupational exposure assessment was based on risk mitigation measures currently implemented on American labels (e.g. reduced rate, one application per season, early season application.)

Mixer, Loader and Applicator Exposure and Risk Assessment
There are potential exposures to mixers, loaders and applicators. The following supported uses were assessed:

- mixing/loading wettable powder in water-soluble packaging for application to orchard crops; and
- applying wettable powder as sprays to orchard crops by airblast.

Based on the limited number of applications (one per year), workers applying formetanate hydrochloride would generally have a short-term (up to 30 days) duration of exposure. The PMRA estimated handler exposure based on different levels of personal protection:

- Maximum personal protective equipment (PPE) (chemical-resistant coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves) plus a respirator, open cab airblast and closed mixing (water-soluble packaging).

- Maximum PPE plus a respirator and chemical-resistant headgear for applicators, open cab and closed mixing (water-soluble packaging).

- Engineering controls: closed cab with baseline PPE (a long-sleeved shirt and long pants, chemical-resistant gloves) and closed mixing (water-soluble packaging) with maximum PPE plus a respirator.

Mixer/loader/applicator exposure estimates are based on the best available data at this time. The assessment might be refined with exposure data representative of modern application equipment and engineering controls. Biological monitoring data could also further refine the assessment.

No acceptable chemical-specific handler exposure data were submitted for formetanate hydrochloride; therefore, dermal and inhalation exposures were estimated using data from the Pesticide Handlers Exposure Database (PHED), Version 1.1. The PHED is a compilation of generic mixer/loader applicator passive dosimetry data with associated software that facilitates the generation of scenario-specific exposure estimates based on formulation type, application

equipment, mix/load systems and level of PPE. In most cases, the PHED did not contain appropriate data sets to estimate exposure to workers wearing chemical-resistant coveralls or a respirator. This was estimated by incorporating a 90% clothing protection factor for chemical-resistant coveralls and 90% protection factor for a respirator into the unit exposure data. Similarly, a 90% protection factor was applied to head and neck dermal unit exposure values for chemical-resistant headgear. Chemical-resistant headgear includes So'westers, or large brimmed, waterproof hats, and hoods with sufficient neck protection. It is crucial to consider headgear as a mitigation measure for this risk assessment, as closed cab airblast equipment is not always feasible in orchards.

Inhalation unit exposures were based on light inhalation rates (17 litres per minute).

Occupational risk estimates associated with applying, mixing and loading for current label uses exceed the ARI of one, provided engineering controls or PPE are used as summarized in Section 8.0 and Appendix IX. Appendix IV summarizes calculated ARIs for mixers/loaders and applicators.

Postapplication Worker Exposure and Risk Assessment

The postapplication occupational risk assessment considered exposures to workers entering treated agricultural sites. Based on the formetanate hydrochloride use pattern, there is potential for short-term (<30 days) postapplication exposure to formetanate hydrochloride residues for workers.

Chemical-specific dislodgeable foliar residue (DFR) data and activity specific transfer coefficients (TC) were used to estimate postapplication exposure resulting from contact with treated foliage at various times after application. DFR data include the amount of residue that can be dislodged or transferred from a surface, such as the leaves of a plant. A TC is a factor that relates worker exposure to dislodgeable residues. TCs are specific to a given crop and activity combination (e.g. hand harvesting apples, scouting in potato fields) and reflect standard agricultural work clothing worn by adult workers. Postapplication exposure activities include harvesting, thinning, pruning, scouting and irrigating trees.

For workers entering a treated site, restricted-entry intervals (REIs) are calculated to determine the minimum length of time required before people can safely re-enter. An REI is the duration of time that must elapse before residues decline to a level where performance of a specific activity results in exposures above the target MOE (i.e. >300 for short- to intermediate-term exposure scenarios).

One DFR study involving airblast application to citrus trees was available to the USEPA for use in the assessment of worker postapplication exposure. The DFR data were used to estimate DFR values for all fruit trees.

The postapplication risk estimates include a number of conservative inputs such as the assumption that workers are exposed to residues for eight hours a day following an application at the maximum rate.

The occupational assessments could be refined with the following data:

- passive dosimetry or biological monitoring studies to assess mixer/loader/applicator exposure;
- passive dosimetry or biological monitoring studies to assess postapplication worker exposure; and
- dislodgeable or transferable residue study.

With these additional data and information, it is expected that estimated exposure and risk would decrease.

Based on available data, to achieve the target MOEs for postapplication workers, REIs need to be added to the label. Appendix IV summarizes calculated REIs for selected re-entry activities, based on currently available exposure data and the target MOE of 300.

The postapplication risks to re-entry workers performing high-exposure activities, such as thinning, pruning and harvesting of fruit trees, and low-exposure activities, such as scouting of fruit trees, do meet the target MOEs (i.e. MOE < 300) if risk mitigation measures are implemented. The newly calculated REIs do meet the target MOEs and are largely considered agronomically feasible, given the timing of application in relation to the crop cycle.

3.2.3 Non-Occupational Exposure and Risk Assessment

Non-occupational risk assessment is concerned with estimating risks to the general population, including children, during or after pesticide application in and around the home. Given there are no domestic products for formetanate hydrochloride nor are there any residential uses, a non-occupational assessment was not conducted.

3.3 Dietary Risk Assessment

In a dietary exposure assessment, the PMRA determines how much of a pesticide residue, including residues in milk and meat, may be ingested with the daily diet. Exposure to formetanate hydrochloride from potentially treated imports is also included in the assessment. These dietary assessments are age specific and incorporate the different eating habits of the population at various stages of life. For example, the assessments take into account differences in children's eating patterns, such as food preferences and the greater consumption of food relative to their body weight when compared to adults. Dietary risk is then determined by the combination of the exposure and the toxicity assessments. High toxicity may not indicate high risk if the exposure is low. Similarly, there may be risk from a pesticide with low toxicity if the exposure is high.

The PMRA considers limiting use of a pesticide when risk exceeds 100% of the reference dose. The PMRA's Science Policy Note SPN2003-03, *Assessing Exposure from Pesticides, A User's Guide*, presents detailed acute and chronic risk assessments procedures.

Residue estimates used in the dietary risk assessment may be conservatively based on the maximum residue limits (MRL) or the field trial data representing the residues that may remain on food after treatment at the maximum label rate. Surveillance data representative of the national food supply may also be used to derive a more accurate estimate of residues that may remain on food when it is purchased. These include the Canadian Food Inspection Agency's (CFIA) National Chemical Residue Monitoring Program and the United States Department of Agriculture Pesticide Data Program.

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.03), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

For more information on dietary risk estimates or residue chemistry information used in the dietary assessment, see Appendix V and VI.

3.3.1 Determination of Acute Reference Dose

To estimate acute dietary risk, the comparative cholinesterase assay in rats was selected as the critical study for this database. A $BMDL_{10}$ of 0.06 mg/kg bw was established based on brain cholinesterase inhibition in female pups. A total uncertainty factor of 100 is required to account for standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. With respect to the *Pest Control Products Act* factor, all of the required studies relevant to assessing risks to infants and children were available for this assessment. While sensitivity in the young was demonstrated, the *Pest Control Products Act* factor can be reduced from 10-fold to 1-fold based on the rationale provided in the *Pest Control Products Act* Hazard Consideration section above. The ARfD was calculated to be 0.0006 mg/kg bw (0.06 mg/kg bw ÷ 100) and is considered to be protective of all populations including infants and children.

3.3.2 Acute Dietary Exposure and Risk Assessment

Acute dietary risk is calculated considering the highest ingestion of formetanate hydrochloride that would be likely on any one day, and using food consumption and food residue values. A statistical analysis allows all possible combinations of consumption and residue levels to be combined to estimate a distribution of the amount of formetanate hydrochloride residue that might be consumed in a day. A value representing the high end (99.9^{th} percentile) of this distribution is compared to the acute reference dose (ARfD), which is the dose at which an individual could be exposed on any given day and expect no adverse health effects. When the expected intake of residues is less than the ARD, then acute dietary exposure is considered to be acceptable.

Two approaches were used to assess acute dietary risk. In the first approach, limited field trial data as presented in the USEPA Reregistration Eligibility Decision (RED) were used to estimate residues in food. Given there were limitations in the field trial data, a second approach in which monitoring data of residues in Canadian foods collected by the Canadian Food Inspection

Agency was used (Appendix VIII). Using the former approach, dietary exposure represents less than 75% of the ARfD. When using the latter approach, dietary exposure is less than 96% of the ARfD for all subpopulations, with the exception of infants. For infants, dietary exposure is greater than 400% of the ARfD based on the monitoring data, indicating that risk mitigation for dietary exposure is required for this subpopulation.

The major contributors to the acute dietary risk in infants was the consumption of peach baby foods (90% of exposure) and residues of formetanate hydrochloride in peaches imported from Chile. These residues were below current Canadian MRLs and American tolerances. These residues, however, were just below proposed American tolerances for formetanate hydrochloride. The proposed American tolerances have not been promulgated, pending submission of further field trials.

Although the acute dietary risk assessment for formetanate hydrochloride is a refined assessment primarily due to the use of monitoring data and conducting a probabilistic assessment, there are some conservatisms in the assessment. These are as follows:

- the assumption of 100% crop treated in countries other than Canada and the United States;
- the fact that most of the formetanate hydrochloride residues are found on the peel of fruits, but the peels are usually removed when preparing baby food, the highest contributor of formetanate hydrochloride exposure in infants;
- the possibility that formetanate hydrochloride residues may further degrade during cooking—the peaches in most baby foods are cooked; and
- the 99.9th percentile of exposure tends to be an overestimate due to the statistical procedures used in DEEM–FCID™.

Most exposures (from the 99th percentile and lower) are well below exposures at the 99.9th percentile (i.e. 19% of the ARfD). Nonetheless, although only a very small percentage of infants is potentially exposed at the 99.9th percentile, this is a concern that needs to be addressed.

Typically, when risk concerns are identified, risk mitigation measures are considered, such as removal of some uses, changes in rate, discontinuation of product, etc. However, the risk was not driven by Canadian uses of formetanate hydrochloride, and application of typical risk mitigation measures in Canada would not result in decreased risk.

As a first step in mitigating risk due to formetanate hydrochloride exposure, the Canadian MRLs for formetanate hydrochloride will be revisited to reflect the change in use pattern implemented on the American labels since 1999 and will be on Canadian labels as result of this round of re-evaluation. All data submitted to the USEPA for establishing their proposed tolerances as well as any further data requested by the USEPA must be submitted to the PMRA. It would be prudent to implement new MRLs quickly as an indirect way of ensuring that the use of formetanate hydrochloride in Chile is consistent with its uses in Canada and the United States, thereby potentially reducing exposures through the diet for infants.

Other possible data that could be submitted to refine the risk assessment include:

- data to assess the level of residue on peel;
- data to assess the degradation of residue through cooking; or
- monitoring data of residues in baby foods, particularly single serving sample sizes.

3.3.3 Determination of Acceptable Daily Intake

To estimate dietary risk from repeat exposure, the comparative cholinesterase assay in rats was again selected as the critical study for this database. A $BMDL_{10}$ of 0.06 mg/kg bw/day was established based on brain cholinesterase inhibition in female pups. The quick acting and reversible nature of carbamate inhibition is considered justification to default to the acute $BMDL_{10}$, which is lower than the subchronic or chronic NOAELs. In the case of formetanate hydrochloride, chronic daily exposure is considered to reflect a series of ongoing acute exposures, with each causing transient inhibition of cholinesterase. A total uncertainty factor of 100 is required to account for standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability.

With respect to the *Pest Control Products Act* factor, all of the required studies relevant to assessing risks to infants and children were available for this assessment. While sensitivity in the young population was demonstrated, relative to the adults, the *Pest Control Products Act* factor can be reduced from 10-fold to 1-fold based on the rationale provided in the *Pest Control Products Act* hazard consideration section above. The ADI was calculated to be 0.0006 mg/kg bw (0.06 mg/kg bw ÷ 100) and is considered to be protective of all populations including infants and children. Furthermore, although it was questionable whether the mouse oncogenicity study (in which no increase in tumours was observed) was conducted with adequate dose levels, this ADI provides a margin of >160 000 to the highest dose tested. This ADI also provides an approximate margin of >8000 to the NOAEL for pup viability.

3.3.4 Chronic Dietary Exposure and Risk Assessment

Chronic dietary risk was calculated by using the average consumption of different foods and the average residue values on those foods. This expected intake of residues was then compared to the ADI. When the expected intake of residues is less than the ADI, then chronic aggregate dietary exposure is acceptable.

Two approaches were used to assess chronic dietary risk. In the first approach, limited field trial data as presented in the USEPA RED were used to estimate residues in food. Given there were limitations in the field trial data, a second approach was used in which monitoring data of residues in Canadian foods collected by the CFIA were used. With both approaches, exposure represents less than 2% or 0.5%, respectively, of the ADI for all subpopulations and is, therefore, not of concern.

3.3.5 Carcinogenic Dietary Exposure and Risk Assessment

Formetanate hydrochloride was not identified as a carcinogen; therefore, a cancer risk assessment was not conducted.

3.4 Exposure From Drinking Water

3.4.1 Concentrations in Drinking Water

Estimated environmental concentrations (EECs) of formetanate hydrochloride in potential sources of drinking water in Canada were calculated in surface water using Level 2 Pesticide Root Zone Model/Exposure Analysis Modeling System (PRZM/EXAMS) on two reservoir scenarios, orchards in the Okanagan Valley, British Columbia, and orchards in southern Ontario, both assumed to be next to a small drinking water reservoir. Groundwater was not considered because previous modelling showed that formetanate hydrochloride is unlikely to leach to groundwater. The highest application rate, once per year at a rate of 1.29 kg a.i./ha, for peaches, was modelled. Application at various times in the growing season from April to July were considered. The predicted EECs are the concentrations at the reservoir, as opposed to the tap.

Daily (acute) and yearly (chronic) formetanate hydrochloride EEC peak values at the 90th percentile in potential drinking water sources at the reservoir are 7.2 µg a.i./L and 0.035 µg a.i./L, respectively.

3.4.2 Drinking Water Exposure and Risk Assessment

Drinking water exposure was calculated by using acute and chronic drinking water EEC values directly into DEEM-FCID™, Version 2.03. For the acute probabilistic assessment, the full distribution of estimated residues was used. For the chronic assessment, the 90th percentile of yearly average concentrations in surface water (0.035 g a.i./L) was incorporated as a point estimate.

Exposure of formetanate hydrochloride from drinking water was less than exposure from food, and was also less than the ARfD and ADI. Therefore, the PMRA concludes that residues of formetanate in drinking water are not of concern.

3.5 Aggregate Risk Assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential and other non-occupational sources as well as from all known or plausible exposure routes (oral, dermal and inhalation).

Aggregate risk assessment looks at the combined potential risk associated with food, drinking water and residential exposures. Given formetanate hydrochloride does not have any residential uses, the aggregate risk assessment therefore, is from dietary and drinking water exposures only.

The combined exposures from diet and drinking water are compared to the ARfD for the acute assessment (one-day exposure) and the ADI for the chronic assessment. Drinking water exposure was very low compared to dietary exposure. Therefore, the aggregate risks are essentially identical to the dietary risks described Section 3.3.

4.0 Impact on the Environment

In assessing the environmental risk of formetanate hydrochloride, a deterministic approach was used. Risk was characterized by the quotient method, the ratio of the EEC to the effects endpoint of concern. Risk quotient (RQ) value of one is the level of concern. RQ values less than one are considered indicative of a negligible risk of non-target effects occurring, whereas values of one and greater than one are considered to indicate that the level of concern is exceeded and some degree of risk exists for effects on non-target organisms. In cases where risk was determined at a screening level to aquatic organisms, a refined aquatic risk assessment was conducted using water concentrations in runoff as estimated by PRZM/EXAMS modelling. A separate refinement of the aquatic risk from spray drift was also conducted. These refined EECs were used to determine RQ values using the quotient method.

The effects endpoints included both acute and chronic, chosen from the range of toxicity tests on species available. Effects endpoints, chosen from the most sensitive species, were used as surrogates for the wide range of species which can be potentially exposed following treatment with formetanate hydrochloride.

4.1 Environmental Fate

Formetanate hydrochloride is very soluble in water (822 g/L) and has low volatility (1.6×10^{-6} mmHg). The Henry's law constant (1.09×10^{-6} atm/m^3/mole) indicates low volatility from moist soil and water surfaces. The partition coefficient, log K_{ow} of <0.002, indicates that bioaccumulation is unlikely.

Formetanate hydrochloride is highly susceptible to hydrolytic transformation at pH 7 and pH 9 ($t_{1/2}$ < 1 d) but is less susceptible at pH 5 ($t_{1/2}$ = 63 d). Phototransformation appears to be an important route of transformation in both soil and water. Aquatic photolytic transformation studies provided half lives of 7.9 h and 1.1 h, at pH 7 and 9, respectively, but is much slower at pH 5 (666 h). The soil photolytic $t_{1/2}$ is < 3 days on a sandy loam soil at pH 5.9. However, the USEPA suggests that formetanate hydrochloride does not photolyze directly but undergoes a light catalyzed hydrolysis.

Available soil biotransformation data suggest that formetanate hydrochloride is readily biotransformed with a $t_{1/2}$ of <1 week in the dark. Five transformation products were identified but no individual product was present at greater than 5.5% of the applied at any sampling interval. However, there were some uncertainties with the study, such as the extensive reported binding. The one anaerobic soil biotransformation study available showed that anaerobic conditions were not maintained during the study. No aerobic or anaerobic aquatic biotransformation studies were available for review.

Formetanate hydrochloride has moderate mobility in sand, sandy loam, and silt loam soils but is classified as having low mobility in sand "sediment". K_{oc}s were 232, 338, 171 and 620, respectively. In an unaged soil column leaching study, formetanate hydrochloride was mobile in low organic matter loamy sand, slightly mobile in low organic sandy loam, and relatively immobile in 2.3% organic matter loamy sand and 2.5% organic matter sandy loam. Of the applied radioactivity recovered in the leachate, 20–30% was parent, 60% were unidentified polar transformation products, and the remainder was the identified hydrolytic transformation products. No studies were available to determine volatility; however, given its Henry's law constant of 1.09×10^{-6} atm/m^3/mole, formetanate hydrochloride will have low volatility from moist soils and water surfaces.

4.2 Environmental Toxicology

4.2.1 Terrestrial

The LD_{50}s for honeybees exposed to formetanate hydrochloride range from 9.21 to 14.3 µg/bee. A foliage study determined that at 0.52 and 1.03 kg a.i./ha application rates, mortality was 1.33 and 0.44% after 14 h, respectively. A number of field toxicity tests concluded that formetanate hydrochloride exhibited "moderately low" toxicity to bees and may be applied whenever bees are not foraging.

Hardman et al.[6] found that formetanate hydrochloride was "very toxic" to the two mite predators *Typhlodromus pyri* (96.7% mortality) and *Zetzellia mali* (98.3% mortality) and "moderately toxic" to the apple rust mite (*Aculus schlechtendal*, 56.2% mortality).

Studies on acute toxicity of formetanate hydrochloride indicate LD_{50}s of 41.5 mg a.i./kg bw and 11.5 mg a.i./kg bw to northern bobwhite quail and mallard duck, respectively. On a dietary basis, the 8-day LC_{50}s for northern bobwhite quail and mallard duck were 3963 and 1413 mg a.i./kg diet, respectively. On a chronic/reproduction basis the NOEC and LOEC for both northern bobwhite quail and mallard duck were 53 and 160 mg a.i./kg diet, respectively.

The acute oral LD_{50} of formetanate hydrochloride in the rat, *Rattus norvegicus* was 26.4 and 14.8 mg/kg bw in females and males, respectively, making it acutely toxic to this species. In a two year dietary study on rats the LOAEL for systemic effects was 250 mg a.i./kg diet based on decreased body weight and the NOAEL was 50 mg a.i./kg diet. In a chronic reproduction test the parental NOAEL was 50 mg a.i./kg diet based on slight decreases in body weight and inhibition of whole blood and brain cholinesterase. The NOAEL for developmental toxicity was 50 mg a.i./kg diet based on decreased pup weight and viability index.

No information was available to determine toxicity of formetanate hydrochloride to vascular plants.

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[6] Hardman, J.M., J.L., Franklin, D.L. Moreau and N.J. Bostanian. 2003. An index for selective toxicity of miticides to phytophagous mites and their predators based on orchard trials. *Pest Management Science*. 59:1321–1332.

4.2.2 Aquatic

Formetanate hydrochloride is acutely toxic to *D. magna*, the 48-h LC_{50} was 0.09 mg a.i./L. The chronic toxicity results indicate that toxicological effects based on daphnid length first appeared at the 1.1 µg a.i./L level and the NOEC was 0.5 µg a.i./L. The LD_{50}s for bluegill sunfish and rainbow trout are 2.7 mg a.i./L and 4.4 mg a.i./L, respectively. An early life-stage toxicity test exposing fathead minnows (*Pimephales promelas*) for 32 days resulted in a NOEC and a LOEC for larval survival of 0.48 and 0.82 mg a.i./L, respectively. No information on toxicity to freshwater algae or vascular plants was available for review.

Formetanate hydrochloride is acutely toxic to all estuarine/marine invertebrate species tested, Eastern oyster (*Crassostrea virginica*), grass shrimp (*Palaemontes vulgaris*) and shore crab (*Pachygrapsus crassipes*); LC_{50}/EC_{50}s were 2.3, 2.5 and 6.8 mg a.i./L, respectively. No information on toxicity of formetanate hydrochloride to marine invertebrates on a chronic basis was available for review. No information on the acute or chronic toxicity of formetanate hydrochloride to estuarine/marine fish, algae or vascular plants was available for review.

4.3 Concentrations in Drinking Water

EECs of formetanate hydrochloride in groundwater were calculated using the LEACHM model and concentrations in surface water were calculated using PRZM/EXAMS models. Pesticide concentrations in surface water were estimated in two types of vulnerable drinking water sources, a small reservoir and a prairie dugout. Results from PRZM/EXAMS predicted that the acute (yearly peak) and chronic (yearly average) concentrations of formetanate hydrochloride at the 90th percentile resulting from runoff were 140 and 0.81 µg a.i./L for reservoirs and 57 and 0.50 µg a.i./L for dugouts, respectively, following use of formetanate hydrochloride at the maximum application rate that was specified on the label (6.4 kg a.i./ha). Results from LEACHM predicted that no residues of formetanate hydrochloride would reach groundwater.

A level 2 EEC modelling assessment for formetanate hydrochloride in potential sources of drinking water was also conducted. EECs in surface water were calculated using the PRZM/EXAMS model, using a proposed application rate of 1.29 kg a.i./ha on peaches in orchards in the Okanagan Valley, British Columbia, and orchards in southern Ontario, both assumed to be next to a small drinking water reservoir. Groundwater was not considered because previous modelling showed that formetanate hydrochloride is unlikely to leach to groundwater. Only the results from the model run with the highest EEC are reported.

Results from PRZM/EXAMS predicted that the concentrations of formetanate hydrochloride in reservoirs at the 90th percentile resulting from runoff were 7.2 and 0.035 µg a.i./L for acute (yearly peak) and chronic (yearly average), respectively. It is important to note that these values represent concentrations at a water intake (reservoir), not at the tap. Because formetanate hydrochloride hydrolyses quickly (the modelling used a half-life of 1 day), it is likely to undergo significant hydrolysis between the time it leaves the reservoir and the time it gets to a tap. There were no water monitoring data from Canada. Water monitoring data were available from the United States and showed no detections. However, the data were limited and was based on sampling carried out in California, Florida, Louisiana and Pennsylvania, two sites per state.

Sampling was from January to April, and there was no indication if or when any formetanate hydrochloride had been applied in the vicinity of the sampling sites.

4.4 Terrestrial Risk Assessment

According to Atkins[7], the LC_{50} for bees (in µg a.i./bee) can be directly converted to the number of kilograms per hectare or application rate by multiplying by 1.12. Using the LD_{50}s of 9.21–14.3 µg/bee the application rate that would kill 50% of the bees is 10.3 to 16.0 kg a.i./ha. Therefore, there is negligible risk of acute adverse effects to honeybees at the proposed application rate of 1.29 kg a.i./ha.

Using a toxicity classification system based on the International Organization for Biological Control Hardman et al. found that formetanate hydrochloride was "very toxic" to two mite predators, *Typhlodromus pyri* (96.7% mortality) and *Zetzellia mali* (98.3% mortality) and "moderately toxic" to the apple rust mite (*Aculus schlechtendal*, 56.2% mortality) when applied on the surface of apple leaves at 1013 g a.i./ha. They classified formetanate hydrochloride as "unfavourably selective" to predaceous mites because it was more toxic to the predators than to the pest species it was used to control. The application rate they used is 277 g a.i./ha lower than the rate of 1.29 kg a.i./ha. This indicates that the insect predators of pests are at risk from all application rates and uses of formetanate hydrochloride, including the application rate of 1.29 kg a.i./ha.

The two common bird species that are used in toxicity studies are the northern bobwhite quail and mallard duck. Although these birds have been known to visit fruit orchards where formetanate hydrochloride will be applied, there are other bird species that visit more frequently or reside in orchard areas. Extrapolation of the toxicity endpoints to these other species is necessary to fully understand the potential risk to wild birds from exposure to formetanate hydrochloride. Mineau et al.[8] determined that the acute toxicity endpoints (LD_{50}) of the standard study species can be extrapolated to other species on a weight basis raised to the power of 1.15 using the following equation $LD_{50(2)} = (W_2/W_1)^{(1.15-1)} \times LD_{50(1)}$.

Assuming birds consume nothing but food oversprayed with formetanate hydrochloride applied at the rate of 1.29 kg a.i./ha, the bobwhite quail would require 2.04 days of food consumption to reach the LD_{50}, the mallard duck would require 6.3 days of food consumption to reach the LD_{50}, the American robin would require 0.35 days of food consumption to reach the LD_{50} and the field sparrow would require 0.30 days of food consumption to reach the LD_{50}. This indicates that it would take less than one day of feeding for small birds to reach their LD_{50} levels. However, currently there are no data available on small birds to confirm our extrapolations on the acute toxicity. Our assessment could also be overly conservative due to the fact that formetanate

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7 Atkins, E.L., D. Kellum and K.W. Atkins. 1981. *Reducing Pesticide Hazards to Honeybees: Mortality Prediction Techniques and Integrated Management Strategies*. University of California, Division of Agricultural Sciences, Leaflet 2883, 22 pp.

8 Mineau, P., B.T. Collins and A. Baril. 1996. On the Use of Scaling Factors to Improve Interspecies Extrapolation of Acute Toxicity in Birds. *Regulatory Toxicology and Pharmacology*. 24: 24–29.

hydrochloride has rapid photolytic and hydrolytic transformation. These factors indicate it is unlikely that birds will receive a dose equivalent to their LD_{50} in one day. In addition, the actual risk to small birds would be less than predicted as food ingested in the natural environment will not be 100% contaminated.

The use of formetanate hydrochloride at 1.29 kg a.i./ha shows negligible risk to wild birds from consumption of food contaminated with formetanate hydrochloride on a dietary basis. There is also a negligible chronic reproductive risk to wild birds associated with the proposed rate of 1.29 kg a.i./ha formetanate hydrochloride.

The number of days feeding on formetanate hydrochloride contaminated food required to reach the acute oral no observed effect level of the rat is less than one day; therefore, terrestrial mammals are at potential risk from formetanate hydrochloride. There is also a risk to mammals from exposure of formetanate hydrochloride on a chronic dietary and reproductive basis from the use of formetanate hydrochloride. However, this assessment could also be overly conservative due to the fact that formetanate hydrochloride has rapid photolytic and hydrolytic transformation. These factors indicate it is unlikely that mammals will receive a dose equivalent to their no observed effect level in one day. In addition, the actual risk to small mammals would be less than predicted as food ingested in the natural environment will not be 100% contaminated.

No information was available to determine toxicity of formetanate hydrochloride to vascular plants; therefore, no risk could be assessed.

4.5 Aquatic Risk Assessment

4.5.1 Screening Level Risk Assessment

The initial aquatic assessment conducted is a deterministic screening level risk assessment. This approach is conservative, and primarily designed to identify the taxonomic groups which are not at risk and/or the use scenarios which do not pose an unacceptable risk. The screening level EEC is a conservative exposure estimate determined as the concentration resulting from a direct application to a 15 or 80 cm depth of water. The endpoints used for acute toxicity were half the LC_{50} for aquatic invertebrates and 1/10th of LC_{50} for fish. Surrogate data from fish studies were used for amphibians as toxicity data on the latter were not available. Environmental risk is characterized using the quotient method which is the ratio of the EEC divided by toxicity endpoint. If the RQ from this analysis is <1 then it can be concluded that there is negligible risk and no further refinement is necessary. The proposed application rate of 1.29 kg a.i./ha was used to determine aquatic EECs. The RQs for freshwater invertebrates were >1 on both an acute and chronic basis. All other aquatic biota including freshwater fish (acute and chronic) and marine/estuarine invertebrates (acute basis) showed negligible risk (RQs <1) associated with formetanate hydrochloride use at the proposed application rate. A refined risk assessment was then conducted to determine risk associated with drift and runoff.

No toxicity endpoints were available for freshwater algae or vascular plants on either an acute or chronic basis, marine or estuarine invertebrates on a chronic basis, or marine/estuarine fish, algae or plants; therefore, risk quotients could not be calculated.

4.5.2 Refined Assessment based on the Potential Risk from Drift

It was estimated from the data of Ganzelmeier et al.[9] (1995) that the 95th percentile deposit into an aquatic habitat adjacent to an orchard sprayed using airblast equipment will not exceed 74% of the applied application rate for early applications and 59% of the applied application rate for late applications. This information was used to estimate peak concentrations in a model water body 80 cm deep adjacent to a field where formetanate hydrochloride was being applied using airblast sprayers. The model water body 80 cm deep was chosen because it was the model water body used to estimate concentrations resulting from runoff using the fate models PRZM/EXAMS. Using this percent drift, the off-site EECs for formetanate hydrochloride were re-calculated. The toxicology endpoints used to calculate risk quotients were the same as those used in the screening level assessment.

The EECs of formetanate hydrochloride in an 80 cm pond due to spray drift would be 0.12 and 0.09 mg a.i./L in early and late season applications, respectively, at the proposed application rate Although the refined risk assessment showed a decrease in the RQ values, the level of concern was still exceeded for freshwater invertebrates on both an acute and chronic basis

4.5.3 Refined Assessment Based on the Potential Risk from Runoff

Aquatic organisms can also be exposed to formetanate hydrochloride as a result of runoff. EECs for a Level 1 receiving water body runoff scenario for aquatic risk assessment were simulated using PRZM/EXAMS models. The water body in the scenario consists of a one hectare wetland with an average depth of 0.80 m and a 10 hectare drainage area. Four geographic scenarios were simulated: an apple orchard in British Columbia, Nova Scotia and Quebec, and vineyard in the Niagara region of Ontario. The model was run for 20 years for all scenarios. The EECs with the appropriate time periods were used to calculate the risk quotients, e.g. 96-hour averages for acute endpoints and yearly averages for chronic endpoints. The toxicology endpoints used to calculate risk quotients were the same as those used in the screening level and refined drift assessments. The level of concern was not exceeded on either an acute or chronic basis for all biota in all modelled scenarios.

4.6 Environmental Assessment Conclusions

Formetanate hydrochloride poses a risk to some terrestrial organisms. Predatory insects are more susceptible to formetanate hydrochloride than the target pest species. The risk assessment for small birds and mammals indicate that these species may be at risk with the use of formetanate

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[9] Ganzelmeier, H., et al. 1995. Studies on the spray drift of plant protection products: Results of a test program carried out throughout the Federal Republic of Germany. Report Number 305 from the Biologischen Bundesanstalt fur Land-und Forstwirtschaft, Berlin-Dahlem. Blackwell Wisseschafts-Verlag GmbH, Berlin/Vienna.

hydrochloride even at the lowest proposed application rate of 1.29 kg a.i./ha. However, the assessment could be overly conservative due to the fact that formetanate hydrochloride has rapid photolytic and hydrolytic transformation. These factors indicate that it is unlikely that small birds and mammals will receive a lethal dose in one day. In addition, the actual risk to small birds and mammals would be less than predicted as food ingested in the natural environment will not be 100% contaminated.

Formetanate hydrochloride also poses a risk to some aquatic organisms. The screening level risk assessment showed that the level of concern was exceeded on both an acute and chronic basis for freshwater invertebrates, however, freshwater fish (on an acute and chronic basis) and marine invertebrates (on an acute basis) were at negligible risk. The refined risk assessment indicated a reduced level of risk. The concentrations of formetanate hydrochloride expected in water due to drift resulted in a reduction of acute and chronic risk for freshwater invertebrates, although the level of concern was still exceeded. There was also no risk for any biota associated with the model-estimated concentrations of formetanate hydrochloride in runoff at the 1.29 kg a.i./ha application rate.

4.7 Environmental Risk Mitigation

4.7.1 Terrestrial Organisms

There is negligible risk of acute adverse effects to honeybees at the proposed application rates. However, formetanate hydrochloride would be of direct harm to naturally occurring predators when these are used as part of an IPM program. To reduce harm to beneficial predators and parasites, spray drift from applications of formetanate hydrochloride should be minimized to reduce harmful effects on beneficials.

The toxicity data indicate that formetanate hydrochloride is toxic to avian species and mammals on an acute basis. There are currently no available options to mitigate the potential risk to birds and small mammals. However, the assessment is considered to be conservative and it is unlikely that small birds and mammals will be exposed to formetanate hydrochloride at sufficient concentrations to result in risk.

Consequently, label statements are recommended to protect terrestrial organisms, and are listed in Appendix IX.

4.7.2 Aquatic Organisms

The toxicity data indicates that formetanate hydrochloride is toxic to freshwater invertebrates, freshwater fish and marine/estuarine invertebrates. Therefore, appropriate precautionary label statements are proposed. To reduce exposure to aquatic organisms buffer zones were calculated for two water body depths (<1 m and >1 m). The applicator will be required to determine the depth of the body of water adjacent to the treatment field prior to application and apply the appropriate buffer zone. The resulting buffer zones (listed in Appendix IX) were calculated only for the proposed lower application rate of 1.29 kg a.i./ha.

Label statements to reduce exposure to aquatic organisms are listed in Appendix IX.

5.0 Value

5.1 Restricted Class Products

All formetanate hydrochloride uses are supported by the registrant. The risk concerns identified in the assessments for the registered uses are mitigable. Consequently, no alternatives to the use of formetanate hydrochloride were considered.

6.0 Toxic Substances Management Policy Considerations

6.1 Toxic Substances Management Policy

During the review of formetanate hydrochloride the PMRA has taken into account the federal Toxic Substances Management Policy and has followed its Regulatory Directive DIR99-03. It has been determined that formetanate hydrochloride does not meet TSMP Track 1 criteria because:

- The log *n*-octanol–water partition coefficient (log K_{ow}) is <0.002 which is below the TSMP Track 1 cut-off criterion of log K_{ow} ≥5.0, it is not bioaccumulative (bioconcentration factors s in whole fish and fillets were <1).

- Formetanate hydrochloride does not meet the criteria for persistence as its half-life values in water (<1–63 days), and soil (<7 days) are below the TSMP Track 1 cut-off criteria for water (≥182 days), sediment (≥182 days) and soil (≥182 days). No data were available to determine persistence of formetanate hydrochloride in air or sediment.

- Formulant issues are being addressed through the PMRA formulant initiatives and Regulatory Directive DIR2006-02, *Formulants Policy and Implementation Document*, published 31 May 2006.

7.0 Summary

7.1 Human Health and Safety

7.1.1 Occupational Risk

Risk estimates associated with applying, mixing and loading activities for label uses are not of concern, provided engineering controls or personal protective equipment are used. Postapplication risks for re-entry workers were not of concern when the proposed mitigation measures are applied.

7.1.2 Dietary Risk from Food

With the exception of infants, acute and chronic dietary risk assessments demonstrate that there were no dietary concerns for any population subgroup in Canada, including children, teenagers, adults and seniors. In addition, no dietary concerns were evident for nursing or pregnant females or based on gender in general.

For infants, the chronic dietary risk assessment was acceptable. However, for acute exposures, risk mitigation is required.

7.1.3 Dietary Risk from Drinking Water

Acute and chronic risk assessments of exposure from drinking water indicated that there were no risk concerns.

7.1.4 Residential Risk

Given there are no residential uses of formetanate hydrochloride, a risk assessment for this scenario was not conducted.

7.1.5 Aggregate Risk

Aggregate risk from combined exposures from diet and drinking water indicated that exposure from drinking water was very low compared to dietary exposure. Therefore, the aggregate risks are essentially identical to the dietary risks described Section 7.1.2.

7.2 Environmental Risk

Formetanate hydrochloride is expected to be non-persistent in soil and aquatic environments. Formetanate hydrochloride poses a risk to aquatic organisms like freshwater invertebrates and terrestrial beneficial predatory insects and mites. To minimize potential exposure to these biota, buffer zones and appropriate label statements are required.

Birds and small mammals could be at risk from use of formetanate hydrochloride. However, the risk assessment is considered to be overly conservative due to the fact that formetanate hydrochloride has rapid photolytic and hydrolytic transformation.

8.0 Proposed Regulatory Decision

The PMRA is proposing that formetanate hydrochloride is acceptable for continued registration with the implementation of the proposed risk-reduction measures. These measures are required to further protect human health and environment. As a condition of the continued registration of formetanate hydrochloride, the new risk-reduction measures must be included on the labels of all products and additional data are required. The proposed label amendments are listed in Appendix IX.

8.1 Proposed Regulatory Actions

8.1.1 Proposed Regulatory Action Related to Human Health

The PMRA has determined that worker risks during mixing, loading and application and during postapplication activities are acceptable, provided that the proposed mitigation measures are implemented. The PMRA has also determined that dietary and drinking water risks are acceptable for all population groups except infants, indicating that risk mitigation for dietary exposure is required beyond the label statements already proposed. Given changes in the use pattern of formetanate hydrochloride and as a result of the dietary risk assessment, the MRLs for formetanate hydrochloride need to be re-evaluated and revised.

8.1.1.1 Toxicological Information

Labels of pesticide products carry statements regarding symptoms of poisoning and treatment, which are especially important for those who may be overexposed when working with the product in a commercial or industrial setting, e.g. mixers/loaders who handle more concentrated forms. Based on the toxicological assessments, the label text of the formetanate hydrochloride-containing products should be expanded and/or standardized, as indicated in Appendix IX.

8.1.1.2 Proposed Mitigation for Dietary Exposure

As a first step in mitigating risk due to formetanate hydrochloride exposure, the Canadian MRLs for formetanate hydrochloride will be revisited to reflect the change in use pattern implemented on the American labels and implemented on Canadian labels.

As the PMRA assessment is based on the same field trials reflecting the American label and these field trials will also be the basis of the PMRA's re-evaluation of MRLs, the Canadian label and proposed mitigation measures need to be consistent with the American label. Therefore the following mitigation measures are proposed:

- Reduction of the number of applications to once per growing season for all crops.
- Reduction of the current maximum application rate to 1.40 kg product/ha or 1.29 kg a.i./ha for all crops.
- Removal of late season applications. Specifically, not to apply after petal fall for pome fruit and stone fruit.

The PMRA welcomes comments on the feasibility of the timing for the early season application.

8.1.1.3 Proposed Mitigation for Mixer, Loader and Applicator Exposure and Postapplication Exposure

The occupational risk assessment was based on the proposed risk mitigation measures above for dietary exposure. In addition, the registrant had agreed to remove all aerial applications of formetanante hydrochloride and to package the product in water-soluble bags.

Based on the above considerations and/or in order to meet the target MOE of 300 and/or ARI of 1.0 in worker populations, the following mitigation measures in addition to those listed above are proposed:

- Removal of aerial applications.
- Water-soluble packaging.
- Additional PPE and/or engineering controls for mixing/loading and applying.
- Restricted-entry intervals for postapplication activities.

8.1.1.4 Residue Definition for Risk Assessment and Enforcement

Division 15, Table II, of the Food and Drug Regulations currently identifies the parent compound formetanate hydrochloride {m-[[(dimethyllamino) methylene]amino] phenyl methylcarbamate hydrochloride} as the residue for risk assessment and enforcement. This residue definition is consistent with that of the USEPA.

8.1.1.5 Maximum Residue Limits for Formetanate Hydrochloride in Food

In general, when the re-evaluation of a pesticide has been completed, the PMRA intends to update Canadian maximum residue limits and to remove MRLs that are no longer supported. The PMRA recognizes, however, that interested parties may want to retain an MRL in the absence of a Canadian registration to allow legal importation of treated commodities into Canada. The PMRA requires similar chemistry and toxicology data for such import MRLs as those required to support Canadian food use registrations. In addition, the Agency requires residue data that are representative of use conditions in exporting countries, in the same manner that representative residue data are required to support domestic use of the pesticide. These requirements are necessary so that the PMRA may determine whether the requested MRLs are needed and to ensure they would not result in unacceptable health risks.

After the revocation of an MRL or where no specific MRL for a pest control product has been established in the Food and Drug Regulations, subsection B.15.002(1) applies. This requires that residues do not exceed 0.1 ppm and has been considered a general MRL for enforcement purposes. Currently, residues of formetanate hydrochloride in all agricultural commodities, including those approved for treatment in Canada are regulated by subsection B.15.002(1). However, changes to this general MRL may be implemented in the future, as indicated in Discussion Document DIS2006-01, *Revocation of 0.1 ppm as a General Maximum Residue Limit for Food Pesticide Residues [Regulation B.15.002(1)]*.

As indicated in Table 8.1.1.5, the Food and Drug Regulations specify MRLs for formetanate hydrochloride residues in citrus, apples, pears, peaches, nectarines and plums. Residues in all other agricultural commodities, including those approved for treatment in Canada but without a specified MRL, must not exceed the general MRL of 0.1 ppm.

As a result of the dietary risk assessment for re-evaluation and given the use pattern of formetanate hydrochloride has been significantly modified in the United States, the PMRA requires data to establish MRLs according to good agricultural practice, as proposed in this

re-evaluation assessment. The data must satisfy requirements as described in Regulatory Directive DIR98-02, *Residue Chemistry Guidelines*. The technical registrant is asked to provide confirmation that residue field trial data for all commodities meet contemporary standards by submitting the appropriate data and/or USEPA Data Evaluation Reports.

Table 8.1.1.5 Formetanate Hydrochloride MRLs in Canada

Commodity	MRL (ppm)
citrus fruits	4
apples, peaches /nectarines, pears	3
plums	0.5

8.1.2 Proposed Regulatory Action Related to Environment

To reduce the effects of formetanate hydrochloride in the environment, mitigation in the form of precautionary label statements, directions for use and buffer zones are required. Environmental mitigation statements are listed in Appendix IX.

8.1.3 Proposed Regulatory Action Relating to Value

At this time, no regulatory action is proposed for formetanate hydrochloride as a consequence of a value assessment.

8.2 Additional Data Requirements

8.2.1 Data Requirements Related to Occupational Exposure Assessment

The following data codes (DACO) are not required as a condition for continued registration of formetanate hydrochloride, but may serve to further refine the risk assessment, thus possibly reducing or removing some restrictions and/or personal protective equipment requirements:

DACO 5.4: Mixer/Loader/Applicator – Passive Dosimetry or DACO 5.5: Mixer/Loader/Applicator – Biological Monitoring
DACO 5.6: Postapplication Worker – Passive Dosimetry or DACO 5.7: Postapplication Worker – Biological Monitoring
DACO 5.9: Dislodgeable/Transferable Residue

8.2.2 Data Requirements Related to Food Residue Chemistry

Under DACO 6 and 7, the following data must be submitted for continuing registration of formetanate hydrochloride.

All residue data including field trials submitted to the USEPA must be submitted to the PMRA within one year of the final re-evaluation decision document. This includes, but is not limited to,

all field trials in stone fruit, pome fruit, citrus fruit; plant and livestock metabolism studies; food processing studies; analytical methodology studies; and storage stability studies. To facilitate the PMRA review, it is highly recommended that USEPA Data Evaluation Reports of these studies be submitted also.

In addition, all residue data including field trials to be submitted to the USEPA as a result of their evaluation as outlined in the document *Formetanate Hydrochloride HED Revised Chemistry Chapter of the RED: Summary of Analytical Chemistry and Residue Data (Phase 4)* must be submitted to the PMRA within one year of the final decision document. This includes but is not limited to all field trials in stone fruit, pome fruit, citrus fruit and clarifications for plant metabolism studies.

Other possible data that could be submitted to refine the risk assessment include:

- data to assess the level of residue on peel;
- data to assess the degradation of residue through cooking; or
- monitoring data of residues in baby foods, particularly single serving sample sizes.

List of Abbreviations

µg	microgram(s)
°C	degree(s) Celsius
a.i.	active ingredient
AGDISP	AGricultural DISPersal
atm	atmospheres
BChE	brain cholinesterase
$BMDL_{10}$	benchmark dose level
bw	body weight
cm	centimetre(s)
CFIA	Canadian Food Inspection Agency
ChE	cholinesterase
DACO	data code
DEEM®	Dietary Exposure Evaluation Model
DFR	dislodgeable foliar residue
DT_{50}	dissipation time to 50% (the dose required to observe a 50% decline in the test population)
DWLOC	drinking water level of comparison
EC_{50}	effect concentration 50%
EChE	erythrocyte cholinesterase
EXAMS	Exposure Analysis Modeling System
F_0	parental generation
F_1	first filial generation
F_2	second filial generation
FCID	Food Commodity Intake Database
g	gram(s)
ha	hectare(s)
HC_5	hazardous concentration above which 95% of aquatic invertebrate species are protected
HCl	hydrochloride
Hg	mercury
kg	kilogram(s)
K_{oc}	organic carbon partition coefficient
K_{ow}	*n*-octanol–water partition coefficient
LC_{50}	lethal concentration to 50% (a concentration causing 50% mortality in the test population)
LD_{50}	lethal dose to 50% (a dose causing 50% mortality in the test population)
L	litre(s)
LOAEL	lowest observed adverse effect level
LOEC	lowest observed effect concentration
LPM	litres per minute
m	metre(s)
m^3	metre(s) cubed
mg	milligram(s)
M/L	mixer/loader
M/L/A	mixer/loader/applicator

mm	millimetre(s)
MOE	margin of exposure
mol	mole
MRL	maximum residue limit
N/A	not applicable
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
Pa	Pascal(s)
PChE	plasma cholinesterase
pH	-log10 hydrogen ion concentration
PHED	Pesticide Handlers Exposure Database
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PPE	personal protective equipment
ppm	parts per million
PRZM	Pesticide Root Zone Model
REI	restricted-entry interval
RQ	risk quotient
SF	safety factor
TSMP	Toxic Substances Management Policy
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet
WSP	water-soluble packaging

Appendix I Registered Formetanate Hydrochloride Products as of 12 May 2008

Registration Number	Class	Registrant	Product Name	Formulation Type	Guarantee
25326	Technical	Gowan Company	Formetanate Hydrochloride Technical	Soluble Powder	92 %
11144	Restricted	Gowan Company	Carzol SP-Miticide-Insecticide Soluble Powder	Soluble Powder	92 %

Appendix II Canadian Registered Uses of Formetanate Hydrochloride

Site(s)	Pests(s)	Marketing Class	Formulation Type	Application Methods and Equipment	Registrant Support for Uses and Identification of Minor Uses
All registered uses of formetanate hydrochloride are supported by the registrant. Aerial application is not supported.					
Use-Site Category 14: Terrestrial Food Crops					
Apple	White apple leafhopper	Restricted	Soluble powder	Ground: hydraulic sprayers, airblast	Y
				Aerial: hydraulic sprayers	N
Apple, pear	European red mite			Ground: hydraulic sprayers, airblast	Y
				Aerial: hydraulic sprayers	N
	Twospotted spider mite			Ground: hydraulic sprayers, airblast	Y
				Aerial: hydraulic sprayers	N
Peach, nectarine	European red mite			Ground: hydraulic sprayers, airblast	M, Y
				Aerial: hydraulic sprayers	M, N
	Twospotted spider mite			Ground: hydraulic sprayers, airblast	M, Y
				Aerial: hydraulic sprayers	M, N

[1] Y = use is supported by the registrant, N = use is not supported by the registrant. For partial support see comments for details, M = use was registered as a User Requested Minor Use Label Expansion (URMULE).

Appendix III Toxicology Assessment for Formetanate Hydrochloride

Table 1 Toxicology Profile for Formetanate Hydrochloride

NOTE: Effects noted below are known or assumed to occur in both sexes unless otherwise specified.

Study/Species/ # of Animals per Group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Metabolism/Toxicokinetic Studies			
Absorption, distribution, metabolism and excretion Rats	^{14}C-labelled Formetanate HCl 1.8 mg/kg bw		**Absorption:** Peak concentration occurs at 6 hours (28 ppm). **Distribution:** 0.178 ppm in liver, <0.1 ppm in other tissues. **Metabolism:** Organosoluble metabolites accounted for 39% of total urinary activity at 6 hours. Water-soluble metabolites made up 61% of total activity at 6 hours, 80% at 72 hours with most of the activity residing in a m-acetamidophenol conjugate. The primary metabolites were determined to be: m-aminophenol, m-formamino-phenyl-N-methylcarbamate and m-formaminophenol. **Excretion:** ~86% in urine, 8% in feces by 72 hrs.
Acute Toxicity Studies			
Acute oral toxicity Mice	Formetanate HCl and formetanate technical		LD_{50}: 13–25 mg/kg bw Clonic convulsions, tremors, body stiffening, lacrimation and salivation. Cholinesterase inhibition within 5 min, with an almost full recovery in 24hrs. Deaths occur after 5 min–3 hrs. **High Toxicity**
Acute oral toxicity Rats	Formetanate HCl and formetanate technical		LD_{50}: young adult 20.5 mg/kg bw [26.4 mg/kg bw (♂), 14.8 mg/kg bw (♀)] 14-days old 21.2 mg/kg bw 5-days old ≈9.0 mg/kg bw 1-days old 4.62 (♀), <4.62 (♂) mg/kg bw Hypoactivity, muscular weakness, lacrimation, exophthalmos, chewing motions, salivation, fibrillations, Straub tail, tremors, convulsions and body stiffening. **High Toxicity**
Acute oral toxicity Dogs	Formetanate technical		LD_{50}: 19 mg/kg bw Salivation, tremors, muscle spasms and lethargy. **High Toxicity**
Acute dermal toxicity Rats	Formetanate technical		LD_{50} >5600 mg/kg bw Salivation, apathy **Low Toxicity**
Acute dermal toxicity Rabbits	Formetanate technical		LD_{50} >4000 mg/kg bw **Low Toxicity**

Study/Species/ # of Animals per Group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Acute inhalation toxicity Rats	Formetanate HCl dust exposure	LC_{50} = 3.65 mg/L (1-hour) Tremors, exophthalmos, nasal discharge, salivation and dyspnoea. **Low Toxicity**	
Acute inhalation toxicity Rats	Formetanate technical dust exposure	LC_{50} = 0.29 mg/L (4-hour) Bloody nasal and ocular discharges, hyperemia and consolidatin of lungs. **Moderate Toxicity**	
Acute inhalation toxicity Rats	Formetanate technical aerosol exposure	LC_{50} = 2.8 mg/L (4-hour) **Low Toxicity**	
Eye irritation Rabbits	Formetanate HCl	**Moderately irritating**	
Dermal sensitization Guinea pig	Formetanate HCl	**Sensitizer in Buehler test**	
Subchronic Toxicity Studies			
29-day toxicity Beagle dogs 1/sex	Purity N/S Formetanate HCl 0, 10, 50, 250, 500 ppm in diet (~0, 0.25, 1.25, 6.25, 12.5 mg/kg bw/day)		≥1.25 mg/kg bw/day: coughing, trembling, salivation, unsteady gait and vomiting. ≥12.5 mg/kg bw/day: small gradual loss in weight. BChE was unaffected. **Note:** Considered supplementary; pilot study to determine dose levels for one-year study.
1-year toxicity Beagle dogs 6/sex/group	Purity 95.7% Formetanate HCl 0, 10, 50, 250 ppm in diet (= 0, 0.37, 1.75, 8.5 mg/kg bw/day)	0.37	≥1.75 mg/kg bw/day: excessive salivation, trembling, coughing, vomiting, laboured respiration, ↓ PChE; ↓ EChE (♂). 8.5 mg/kg bw/day: ↓ EChE, thickening of muscular coat of jejunum and pylorus of stomach; ↓ BChE (♂).
21-day dermal toxicity Sprague-Dawley rats 10/sex/group (main study) 10/sex/group (FOB and ChE assessment)	Purity 92.7% Formetanate HCl 0, 10, 15 or 20 mg/kg bw/day in methylcellulose semi-occluded for 6 hours/day, 5 days/week	15	15 mg/kg bw/day: ↓ 9% whole blood ChE (♀) 20 mg/kg bw/day: ↓ 7% whole blood ChE (♂) No systemic effects NOAEL for ChE inhibition established in conjunction with single dose dermal study

Study/Species/ # of Animals per Group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Neurotoxicity Studies			
Acute neurotoxicity Sprague Dawley rats 10/sex/group (main study) 5/sex/group (ChE study)	Purity 92.8% Formetanate HCl 0, 0.1, 1, 10 mg/kg bw by gavage	0.1	≥1 mg/kg bw: ↓cerebral cortex, hippocampus and cerebellum ChE; ↓whole blood ChE, ↓PChE (♂) 10 mg/kg bw: slight to moderate tremors, slight to moderate ataxic gait, slight to extreme gait incapacity, very slight to slight locomotor activity level, severely to moderately ↓ arousal, ↓ rearing, pinpoint pupils, none to slight response to toe or tail pinch, visual placing after vibrissae touch, ↓body temperature, ↓ motor activity; slight to moderate salivation, altered auricular startle response, ↓ forelimb grip strength (♂); ↓whole blood ChE, ↓PChE (♀) All effects noted at time of peak effect (30–60 minutes postdosing)
Time of Peak Cholinesterase (ChE) Inhibition Study and Acute Comparative ChE study Sprague Dawley Adult and Pup (PND 11) Rats. Assessment of EChE and BChE inhibition 5/sex/group/ time point for the time of peak ChE study 10/sex/group per population (adult and pup groups) for the comparative ChE study	Purity 97.8% Formetanate HCl 0, 5.0 mg/kg bw at 15, 30 min and 1 hr to assess time to peak effect; 4, 8 and 24 hrs to assess recovery time 0, 0.65, 1.5 or 3.0 mg/kg bw in deionized water via gavage.	$BMDL_{10}$ 0.06 (♀ pup) 0.07 (♀ adult)	PND 11 Pups 0.65 mg/kg bw: BChE (↓ 34–47%) ; EChE (↓21–30%) 1.5 mg/kg bw: BChE (↓ 68%); EChE (↓29–30%) 3.0 mg/kg bw: BChE (↓ 70–74%); EChE (↓27–29%) Adults 0.65 mg/kg bw: BChE (↓ 16–24%) 1.5 mg/kg bw: BChE (↓ 32–39%) 3.0 mg/kg bw: BChE (↓ 33–50%); EChE (↓29%, ♂) Benchmark dosing results (↓BChE): BMD_{10} 0.09 mg/kg bw (♀ pups) $BMDL_{10}$ 0.06 mg/kg bw (♀ pups) BMD_{10} 0.14 mg/kg bw (♂ pups) $BMDL_{10}$ 0.13 mg/kg bw (♂ pups) BMD_{10} 0.17 mg/kg bw (♀ adults) $BMDL_{10}$ 0.07 mg/kg bw (♀ adults) BMD_{10} 0.29 mg/kg bw (♂ adults) $BMDL_{10}$ 0.06 mg/kg bw (♂ adults) Benchmark dosing results (↓EChE): BMD_{20} 2.09 mg/kg bw (♀ pups) $BMDL_{20}$ 1.17 mg/kg bw (♀ pups)

Study/Species/ # of Animals per Group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
			BMD_{20} 0.47 mg/kg bw (♂ pups) $BMDL_{20}$ 0.17 mg/kg bw (♂ pups) BMD_{20} 4.83 mg/kg bw (♀ adults) $BMDL_{20}$ 1.31 mg/kg bw (♀ adults) BMD_{20} 2.07 mg/kg bw (♂ adults) $BMDL_{20}$ 1.27 mg/kg bw (♂ adults)
Subchronic neurotoxicity Sprague Dawley rats 10/sex/group (main study) 10/sex/group (ChE study)	Purity - 92.8% Formetanate 0, 10, 50 or 300 ppm (= 0, 0.6/0.7, 3.0/3.5 or 18.4/20.9 mg/kg bw/day in ♂/♀) in diet for 13 weeks	3.0/3.5	18.4/20.9 mg/kg bw/day: ↓ body-weight gains (~15–25%); ↓ body weight (~10–13%), ↓ food consumption (♀) No effect on whole blood, plasma and brain cholinesterase, clinical signs, FOB parameters, motor activity, neuropathology or brain weights.
1 and 6-day ChE activity Sprague Dawley rats 10 ♂/group	Purity - 96.0% 4 mg/kg bw by gavage once or 200 ppm in diet for 6 days (~10 mg/kg bw/day)		Gavage administration produced a more marked and more transient depression of whole blood cholinesterase than dietary administration; only the former route produced overt signs of toxicity.
ChE activity Dogs	Purity - N/S 7.5 mg/kg bw		Rapid ↓ in ChE activity, salivation, tremors and dyspnoea with recovery between 80 minutes and 6 hours. Considered supplementary.
Dermal ChE study Sprague Dawley rats 10/sex/group	Purity - 92.5% Formetanate HCl 0, 10, 20 or 500 mg/kg bw in deionized water or 500 mg/kg bw in 1% methyl cellulose on skin for 6 hours	10	20 mg/kg bw: ↓ whole blood ChE (♂) 500 mg/kg bw: one rat with salivation (methylcellulose vehicle), ↓ whole blood ChE (♀) Full recovery by 19 hours postdosing. Time to peak effect was 0.5 to 3 hours post-dosing.
Chronic Toxicity/Oncogenicity Studies			
95-week oncogenicity CD-1 mice 50/sex/group	Purity 94.7–95.7% Formetanate HCl 0, 10, 50, 500 ppm in diet (= 0, 1.4/1.9, 7/9.3, 70/98 mg/kg bw/day in ♂/♀)	9.3	98 mg/kg bw/day: ↓ weight gain, ↓ food conversion (♀) **Note:** Study considered to be marginally adequate assessment of carcinogenic potential as MTD not well-demonstrated. **No evidence of carcinogenicity.**

Study/Species/ # of Animals per Group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
2-year chronic toxicity/ oncogenicity Sprague Dawley rats 50/sex/group + 20/sex/group in 12-month sacrifice groups	Purity 95.1–96% Formetanate HCl 0, 10, 50, 250 ppm in diet (= 0, 0.45/0.58, 2.3/2.9, 12/15 mg/kg bw/day in ♂/♀)	0.45 (♂)	≥0.45 mg/kg bw/day: ↓ BChE (♂) 2.3 mg/kg bw/day: ↓ BChE (♂). 12/15 mg/kg bw/day: ↓ weight gain, ↓ food intake, ↓ whole blood and PChE; ↓ BChE (♀). **Note:** the effect on BChE in ♂ at 0.45 mg/kg bw/day was marginal (~10%) but statistically significant and is thought to be the threshold NOAEL **No evidence of carcinogenicity.**
Reproductive and Developmental Toxicity Studies			
2-Generation reproductive toxicity CR1 rats, 30/sex/group	Purity 95.7% Formetanate HCl 0, 10, 50, 250 ppm in diet (= 0, 0.9, 4.5, 23 mg/kg bw/day)	Parental, reproductive, offspring: 4.5	**Parental:** 23 mg/kg bw/day: ↓ weight gain (F_1 ♀ during gestation); ↓ EChE, ↓ BChE (F_0♂) **Reproductive:** 23 mg/kg bw/day: slight ↓ birth weights (F_2 litters) **Offspring:** 23 mg/kg bw/day: slight ↓ viability (F_2 litters), slight ↓ weight gain (F_2 litters)
Developmental toxicity Sprague Dawley rats 22 ♀/group	Purity 95.7% Formetanate HCl 0, 1, 3, 5 mg/kg bw/day on days 6–15 of gestation by gavage	Maternal: 1 Developmental: ≥5	**Maternal:** ≥3 mg/kg bw/day: ↓ weight gain, salivation, ↓ food intake, slight tremors **Developmental:** No adverse effects reported **No evidence of teratogenicity**
Developmental toxicity NZW rabbits 14 ♀/group	Purity 96% Formetanate HCl 0, 5, 15, 30 mg/kg bw/day on days 6–19 of gestation by gavage	Maternal: 5 Developmental: ≥30	**Maternal:** ≥15 mg/kg bw/day: ataxia, ↓weight gain, ↓food intake. 30 mg/kg bw/day: ↑respiratory rate, salivation, pupillary constriction, muscular tremors and mortality (1). **Developmental:** No adverse effects reported. **No evidence of teratogenicity.**

Study/Species/ # of Animals per Group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Genotoxicity Studies			
Salmonella typhimurium histidine reversion	Purity N/S 0–5000 ug/plate with and without activation	Negative in two assays.	
Reverse mutation in *S.typhimurium* (5 strains), *E.coli* (WP2 uvrA) and *S.cerevisiae* D7	Purity N/S Dose level - N/S with and without activation	Negative.	
Recessive lethality in *D.melanogaster*	Purity N/S Dose level - N/S	Negative.	
Mouse Lymphoma cells L5178Y (tk^+tk^-)	Purity - 96% 0 to 80 µg/ml with and without activation	↑ in mutation frequencies from ≥20 µg/ml without activation and ≥40 µg/ml with activation. Two other studies found to be negative.	
In vitro chromosome analysis Human Lymphocytes	Purity 95.7% 0–500 µg/ml with activation, 0–200 µg/ml without activation; repeat test 60–500µg/ml without activation	A dose-related clastogenic effect in the absence of metabolic activation (only). The most prevalent aberrations observed were chromatid breaks with fragments and acentric fragments.	
HGPRT study in Chinese hamster	Purity N/S Dose level - N/S With and without activation	Negative.	
DNA damage - differential toxicity in *E. coli* (pol A), *B. subtilis* rec. and *S. typhimurium* (uvrB, rec)	Purity N/S Dose level - N/S	Negative.	
DNA damage - mitotic recombination in *S. cerevisiae* (D3)	Purity N/S Dose level - N/S	Negative in two studies.	
DNA damage - gene conversion and cross over in *S. cerevisiae* (D7)	Purity N/S Dose level - N/S	Negative.	
UDS - human lung fibroblasts (W1-38)	Purity N/S Dose level - N/S	Negative.	

Study/Species/ # of Animals per Group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
DNA repair - *E. coli* pol A+ and pol A-, *B. subtilis* recplus and rec- strains	Purity N/S Dose level - N/S	Negative.	
Sister-chromatid exchange - CHO cells	Purity N/S Dose level - N/S	Negative.	
Dominant lethal - mice	Purity N/S Dose level - N/S	Negative.	
Chromosome breakage (micronuclei) mouse bone marrow and cardiac blood	Purity N/S Dose level - N/S	Negative.	
Micronucleus test - Swiss CD-1 mice	Purity 91.5% 9.2 mg/kg bw by gavage	Negative.	
Other Studies			
Ames spot test in *S. typhimurum* his G.46 and an in vivo mouse micronucleus test	Purity N/S In vitro -after N-nitrosation at acid pH. In vivo -10 mg/kg bw formetanate with 50 mg/kg $NaNO_2$	Following N-nitrosation, formetanate was mutagenic in the bacterial spot test but lacked activity in the mammalian in vivo test.	
Acute oral toxicity Rats	Purity N/S Formetanate HCl and six metabolites	LD_{50}: formetanate hydrochloride: 19 mg/kg bw m-aminophenyl-N-methylcarbamate: 218 mg/kg bw m-(((methylamino)methylene)amino)phenyl methyl carbamate (demethyl formetanate): 295 mg/kg bw m-(((dimethylamino)methylene)amino)phenol hydrochloride: 400 mg/kg bw m-formaminophenyl-N-methylcarbamate: 327 mg/kg bw m-formaminophenol: 1830 mg/kg bw m-aminophenol: 1102 mg/kg bw	
Acute oral toxicity Rats	Purity N/S Two metabolites	LD_{50} of desmethylformetanate: young adult: 267 mg/kg bw 14-day old: 290 mg/kg bw 5-day old: 220 mg/kg bw 1-day old: 160 mg/kg bw LD_{50} of m-formaminophenyl-N-methylcarbamate: young adult: 280 mg/kg bw 14-day old: 305 mg/kg bw 5-day old: 280 mg/kg bw 1-day old: 220 mg/kg bw	

Table 2 Toxicology Endpoints for Health Risk Assessment for Formetanate Hydrochloride

Exposure Scenario	Endpoint	Study	Dose (mg/kg bw/day)	CAF[a] or MOE
Acute and Chronic Dietary	ChE inhibition	Comparative Cholinesterase Assay	0.06 ($BMDL_{10}$)	100
	ARfD = 0.0006 mg/kg bw ADI = 0.0006 mg/kg bw/day			
Short/ Intermediate/ Long-term [b] Inhalation [c]	ChE inhibition	Comparative Cholinesterase Assay	0.06 ($BMDL_{10}$)	100
Short/ Intermediate/ Long-term [b] Dermal	ChE inhibition	Acute and 21-day dermal	15	300

[a] Cumulative assessment factor (CAF) refers to total of uncertainty factors and *Pest Control Products Act* factor for dietary assessments, MOE refers to desired margin of exposure for occupational assessments.

[b] Relevant for all durations of exposure.

[c] As an oral $BMDL_{10}$ was selected, an inhalation absorption factor of 100% (default value) should be used in route-to-route extrapolation.

Appendix IV Occupational Exposure Risk Estimates for Formetanate Hydrochloride

Table 1 Occupational Mixer, Loader and Applicator Exposure and Risk Assessment

Crop	Method of Application	Form	Rate[a] kg a.i./ha	Area Treated[b] ha/day	Daily Exposure µg/kg/day		Margins of Exposure		Aggregate Risk Index[g]
					Dermal[c]	Inhalation[d]	Dermal[e]	Inhalation[f]	
Use-Site Category 14: Terrestrial Food Crops									
A. Maximum PPE [h] plus a respirator									
Apples, pears, peaches, nectarines	Airblast	WSP	1.3	16	142.04	0.18	106	338	**0.32**
B. Maximum PPE [h] plus a respirator and chemical-resistant headgear for applicators									
Apples, pears, peaches, nectarines	Airblast	WSP	1.3	16	19.67	0.18	763	338	**1.45**
C. Engineering Controls [i]									
Apples, pears, peaches, nectarines	Airblast	WSP	1.3	16	13.03	0.18	1151	338	**1.8**

[a] Proposed label rate

[b] Based on PMRA default Area Treated Per Day table.

[c] Where dermal exposure µg/kg/day = (unit exposure × area treated × rate)/70 kg bw

[d] Where inhalation exposure µg/kg/day = (unit exposure × area treated × rate)/70 kg bw

[e] Based on a dermal NOAEL of 15.0 mg/kg bw/day

[f] Based on a $BMDL_{10}$ of 0.06 mg/kg bw/day from an oral study

[g] Aggregate Risk Index = $1/((1/RI_D)+(1/RI_I))$. Where RI = Risk Index. RI_D = Dermal MOE/Target Dermal MOE. RI_I = Inhalation MOE/Target Inhalation MOE. Table cells are shaded when the ARI <1.0. If the ARI exceeds 1, the risk is below the level of concern.

[h] Max PPE = Maximum Personal Protection Equipment = Chemical-resistant coveralls over a long-sleeved shirt and long pants with chemical-resistant gloves.

[i] Engineering Controls = Closed cab application with coveralls over long sleeves and long pants with chemical-resistant gloves.

Table 2 Occupational Postapplication Exposure Risk Estimates

Crop	Activity	Transfer Coefficient [a] cm^2/hr	DFR [b] $\mu g/cm^2$	Dermal Exposure [c] µg/kg bw/day	MOE [d]	REI [e]
Use-Site Category 14: Terrestrial Food Crops						
Apples, pears, peaches, nectarines Rate: 1.30 (WSP) kg a.i./ha one application per year	Thinning	3000	0.13	44.5	337	**19**
	Harvesting, propping, pruning, training	1500	0.29	48.92	307	**14**
	Weeding, irrigating, scouting	500	0.39	44.7	336	**12**

[a] Transfer coefficients are from the Science Advisory Council for Exposure Agricultural Transfer Coefficient document (Revised 7 August 2000) and any amendments thereof (PMRA 2004).

[b] DFR data is based on DFR data (see Section 3.5), at X days after application, where X is the day when an MOE ≥300 is determined or the proposed REI.

[c] Dermal exposure = DFR × TC × 8 hr / 70 kg.

[d] Based on the short and intermediate term dermal NOAEL of 15.0 mg/kg bw/day and a target MOE of 300.

[e] Day at which the dermal exposure results in an MOE ≥300.

Appendix V Dietary Exposure and Risk Estimates for Formetanate Hydrochloride

Population Subgroup	Acute Dietary Aggregate (Food and Water) Exposure and Risk at the 99.9th percentile				Chronic Dietary (Food and Water) Aggregate Exposure and Risk			
	Based on Field Trial Data		Based on CFIA Monitoring Data		Based on Field Trial Data		Based on CFIA Monitoring Data	
	Exposure	% ARD	Exposure	% ARD	Exposure	% ADI	Exposure	% ADI
General Population	0.000187	31	0.000186	31	0.000003	0.5	0.000001	0.1
All infants (<1 year old)	0.000448	75	0.002708	451	0.000012	2	0.000003	0.5
Children 1–2 years old	0.00035	58	0.000578	96	0.000007	1.1	0.000002	0.3
Children 3–5 years old	0.000354	59	0.00024	40	0.000006	0.9	0.000001	0.2
Children 6–12 years old	0.000221	37	0.000163	27.1	0.000003	0.6	0.000001	0.2
Youth 13–19 years old	0.000121	20	0.000075	12.5	0.000002	0.3	0.000001	0.1
Adults 20–49 years old	0.000117	20	0.000168	28.1	0.000002	0.4	0.000001	0.1
Females 13–49 years old	0.00012	20	0.000171	28.5	0.000003	0.5	0.000001	0.1
Adults 50+ years old	0.000195	33	0.000173	28.9	0.000003	0.5	0.000001	0.1

Reference Doses:
ARfD = 0.0006 mg/kg bw
ADI = 0.0006 mg/kg bw/day

Appendix VI Food Residue Chemistry Summary

The PMRA based their review of the food residue chemistry on the USEPA evaluations as presented in the following documents:

> USEPA. December 14, 2005. *Formetanate Hydrochloride HED Revised Chemistry Chapter of the RED: Summary of Analytical Chemistry and Residue Data (Phase 4).*
>
> USEPA. December 16, 2005. *Formetanate Hydrochloride: Revised Acute Probabilistic and Chronic Dietary Exposure Assessments for the Reregistration Eligibility Decision.*
>
> USEPA. March, 2006. *Interim Reregistration Eligibility Decision for Formetanate Hydrochloride*. EPA 738-R-06-015.

The USEPA conducted a preliminary health risk assessment for formetanate hydrochloride in 1999 (USEPA RED dated 4/6/99). At that time, the USEPA was concerned that formetanate hydrochloride use presented dietary, occupational and ecological risks. Subsequently, a Memorandum of Agreement (MOA) between the registrant and the USEPA was issued (dated 10/14/99), in which label amendments were required, including reduction of the maximum application rate to 1.15 lb a.i./acre (1.29 kg a.i./ha), limiting the number of applications to once per season, and altering the timing of application to earlier in the season for pome, stone and citrus fruit. These risk mitigation measures were the basis for the reregistration assessments of formetanate hydrochloride by the USEPA, including the submitted residue studies.

The PMRA's dietary assessment was based on the USEPA RED in which field trials reflecting the above mitigation measures were used.

The USEPA concluded that the residue of formetanate hydrochloride in livestock and plants have been adequately delineated. The parent compound was not identified in ruminant and poultry metabolism studies and two cholinesterase-inhibiting metabolites were determined to be not of significant toxicological concern. Therefore, no tolerances are required for formetanate hydrochloride or its metabolites in livestock commodities.

Data from various metabolism studies in plants indicate that the parent compound, formetanate hydrochloride, is the residue of concern in plants.

The required metabolism study in peaches was considered acceptable by the USEPA with the exception that information regarding the storage stability of peach extract was unacceptable. Supporting chromatographic evidence is required by the USEPA.

The registrant submitted field trial data at the new reduced rate specified in the MOA (1.15 lb a.i./acre) for apple, pear, peach, nectarine, orange, grapefruit and lemon. The USEPA considered the residue data limited to support the use pattern of the MOA. Limitations were noted in terms of requirements for bridging studies, number of application rates, and number of field trials in various regions. For the nectarine study (MRID 45071301), details pertaining to field procedures, including application rate and what end-use product was used, were not

provided. The USEPA requires further field trial data as outlined in their RED. Specifically, field trial studies in grapefruit, lemon, lime, orange, tangelo, tangerine, apple, pear, nectarine and peach are required.

The USEPA described two methods for analysis of formetanate hydrochloride and/or metabolites in plant commodities. The first, used for enforcement purposes and referred to as the common moiety method, is gas chromatography/electron capture detection (GC/ECD) Method I listed in the *Pesticide Analytical Manual* Vol. II and involves hydrolysis of residues to 3-aminophenol and therefore, determines residues of formetanate hydrochloride and all metabolites convertible to 3-aminophenol. The limit of quantification (LOQ) for this method is 0.02 ppm for all crops. The second method, submitted by the registrant and referred to as the single analyte method, is a high performance liquid chromatography (HPLC) method that determines residues of formetanate hydrochloride only. The LOQ of this method is 0.1 ppm for nectarines and 0.03 ppm for apples, pears, peaches and citrus. Further data would be required to use the latter method for enforcement purposes.

The USEPA also reviewed apple and citrus processing studies which were considered acceptable. Processing data indicate that residues in apple and citrus juice are reduced by a factor of 0.31× and 0.03× compared to fresh apples and citrus, respectively. A 40× concentration factor for citrus peel was calculated from the data.

The USEPA have established tolerances for formetanate hydrochloride in registered commodities. In the most recent RED, the tolerances were re-assessed based on the limited field trial data performed at the reduced rate and increased PHIs. Tolerances were re-assessed based on results of the HPLC method or the GC/ECD method, whichever resulted in higher residues. Apple processing data indicated that a tolerance must be proposed for residues in apple, wet pomace. As formetanate hydrochloride is no longer used on plums or prunes, its tolerance in these commodities can be revoked. Although the field trials generally reflect the new use pattern for formetanate hydrochloride in the United States, they were considered inadequate to promulgate the proposed tolerances. Tolerances will be reevaluated by the United States when further data are submitted and deemed adequate.

Both the current and proposed USEPA tolerances for formetanate hydrochloride are presented in Appendix VII. This appendix also lists the current Canadian MRLs for formetanate hydrochloride.

Appendix VII Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

An MRL is the maximum concentration of a pesticide that may remain in or on a food at the farm gate when the pesticide is used according to registered label directions. MRLs apply to residues on both food produced in Canada and food imported into Canada from other countries. These MRLs are currently established under the Food and Drug Regulations of the *Food and Drugs Act*, only if Health Canada's Pest Management Regulatory Agency has determined that the consumption of the pesticide residues that could remain on the food as it is eaten will not pose an unacceptable health risk. Actual residues in food as it is eaten are usually much lower than the MRL.

The United States uses the term tolerance to describe pesticide residue limits, while Canada uses the term MRL. Health Canada has worked closely with the USEPA for a number of years, and the two agencies have similar policies and standards that guide the establishment of tolerances and MRLs.

Current Canadian MRLs for formetanate hydrochloride residues are listed in the table below. The residue definition is the parent compound. In this round of reevaluation, the PMRA did not assess the basis for the current MRLs of formetanate hydrochloride.

The USEPA have established tolerances for formetanate hydrochloride in registered commodities. As in Canada, the residue definition is the parent compound. However, as the use pattern of formetanate hydrochloride has changed in the United States the USEPA re-assessed their tolerances based on limited field trial data (see Appendix VI). Although the field trials generally reflect the new use pattern for formetanate hydrochloride in the United States, they were considered inadequate to promulgate the proposed tolerances. Tolerances will be re-evaluated by the United States when further data are submitted and deemed adequate. Both the current and proposed USEPA tolerances for formetanate hydrochloride are listed the table hereafter.

The Codex maximum limit for pesticide residues (Codex MRL) is the maximum concentration of a pesticide residue (expressed as mg/kg), recommended by the Codex Alimentarius Commission to be permitted in or on food commodities and animal feeds. The Codex Alimentarius Commission was established by the Food and Agriculture Organization of the United Nations in 1961. Codex standards are considered reference standards for foods in international trade. There are currently no MRLs for formetanate hydrochloride in Codex.

As the PMRA has proposed that the use pattern of formetanate hydrochloride be modified in Canada similar to that of the United States, and due to the results of the dietary risk assessment, the PMRA will be re-evaluating the MRLs for formetanate hydrochloride and is requesting data for this purpose.

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

Canadian MRLs, Current United States Tolerances and Proposed United States Tolerances for Formetanate Hydrochloride

Crop	Canadian MRLs (ppm)	Current American Tolerances (ppm)	Proposed American Tolerances (ppm)
Apples	3.0	3.0	0.5
Pears	3.0	3.0	0.5
Peaches	3.0	5.0	0.4
Nectarines	3.0	4.0	0.4
Citrus fruit	4.0	–	–
Grapefruit	See citrus	4.0	1.5
Lemon	See citrus	4.0	0.6
Lime	See citrus	4.0	0.03
Orange	See citrus	4.0	1.5
Tangerine	See citrus	4.0	0.03
Plum	0.5	2.0	Revoke
Apple, wet pomace	–	–	1.5
Tangelo	See citrus	–	0.03

Appendix VIII Monitoring Data

Canadian Food Inspection Agency Monitoring Data

The National Chemical Residues Monitoring Program of the CFIA monitors the pesticide residues in domestic and imported foods. The data is compiled, evaluated and summarized in annual reports. This information is also used to determine the priorities of the ongoing monitoring program. The data allows for assessment of gradual changes in the compliance rate, the effectiveness of introduced control measures, and the estimation of consumer exposure to potentially harmful contaminants. On a daily basis, the results reported are compared to Canadian standards (e.g. MRLs). If found in violation, the CFIA undertakes actions deemed appropriate to the risk, up to and including product recall.

Formetanate hydrochloride residues in food were monitored by the CFIA during a two-year period from 2005 to 2007 and are summarized in the table below. Most of the samples were non-detect, with the exception of domestic pears for which 2 samples of 57 had detectable residues and imported peaches and nectarines for which 11 samples out of a total of 175 had detectable residues. All residues are below current MRLs and tolerances. For the dietary assessment, foods identified on labels for application of formetanate hydrochloride in Canada and the United States or which have established MRLs/tolerances were selected, although the CFIA monitored other types of food commodities as well, which were non-detect for formetanate hydrochloride.

Summary of the 2005–2006 CFIA Monitoring Program for Domestic and Imported Commodities

Domestic Food Commodities				
Food Commodities	N° of Samples	N° of Detects	Minimum of Concentration (ppm)	Maximum of Concentration (ppm)
Apple, Fresh	149	0	n/a	n/a
Nectarine, Fresh	19	0	n/a	n/a
Peach, Fresh	42	0	n/a	n/a
Pear, Fresh	57	2	0.1	0.27

Imported Food Commodities				
Food Commodities	N° of Samples	N° of Detects	Minimum of Concentration (ppm)	Maximum of Concentration (ppm)
Apple, Fresh	195	0	n/a	n/a
Grapefruit, Fresh	136	0	n/a	n/a
Lemon, Fresh	80	0	n/a	n/a
Lime, Fresh	28	0	n/a	n/a
Nectarine, Fresh	93	7	0.107	1.43
Orange, Fresh	369	0	n/a	n/a
Peach, Fresh	82	4	0.208	0.394
Pear, Fresh	154	0	n/a	n/a
Plum, Fresh	68	0	n/a	n/a
Tangerine, Fresh	3	0	n/a	n/a

Appendix IX Label Amendments for Products Containing Formetanate Hydrochloride

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Additional information on labels of currently registered products should not be removed unless it contradicts the label statements below.

The Canadian restricted end-use product label for Registration Number 11144 must be amended to include the following changes and statements to further protect human health and the environment.

GENERAL LIMITATIONS

RESTRICTED USES:

The following text in Registration Number 11144:

> **RATE:** 250–500 g per 100 litres of dilute spray (4000–5000L of water per ha) or AT LEAST 1.1 kg per hectare.

must be amended to:

> **RATE:** 250–500 g per 1000 litres of dilute spray (4000–5000L of water per ha) or AT LEAST 1.1 kg per hectare. DO NOT apply more than once per growing season. Apply at a maximum rate of 1.40 kg product/ha equivalent to 1.29 kg a.i./ha for all crops.

The current PHIs must be removed.

The following text in Registration Number 11144:

> Apples, Pears: Apply when mites or insects are first noticed and repeat as needed. Do not apply later than 1 day before harvest on apple and pear. To avoid excessive residue, do not apply more than 4.48 kg per hectare after Calyx.
>
> Peaches, Nectarines: Apply when a threshold of 5–10 active mites per leaf is reached (mid-July to early August). The majority of the mite population should be in the young nymphal stage. Do not apply later than 21 days before harvest. Do not apply more than once per year.

must be amended to:

> Pome fruits (apples and pears): Pesticide products containing the active ingredient formetanate hydrochloride should not be applied after petal fall. Late season applications are not permitted. Apply when mites or insects are first noticed.

Peaches and nectarines: Pesticide products containing the active ingredient formetanate hydrochloride should not be applied after petal fall. Late season applications are not permitted. The majority of the mite population should be in the young nymphal stage.

All instructions related to aerial applications must be removed from the current label.

TOXICOLOGICAL INFORMATION:

Formetanate hydrochloride is a carbamate which is a cholinesterase inhibitor. Typical symptoms of overexposure to cholinesterase inhibitors include malaise, muscle weakness, dizziness and sweating. Headache, salivation, nausea, vomiting, abdominal pain and diarrhea are often prominent. A life-threatening poisoning is signified by loss of consciousness, incontinence, convulsions and respiratory depression with a secondary cardiovascular component. Treat symptomatically. If exposed, plasma and red blood cell cholinesterase tests may indicate degree of exposure (baseline data are useful). However, if a blood sample is taken several hours after exposure, it is unlikely that blood cholinesterase activities will be depressed, due to rapid reactivation of cholinesterase. Atropine, only by injection, is the preferable antidote. Do not use pralidoxime. In cases of severe acute poisoning, use antidotes immediately after establishing an open airway and respiration. With oral exposure, the decision of whether to induce vomiting or not should be made by an attending physician.

PRECAUTIONARY STATEMENTS

PROTECTIVE CLOTHING AND EQUIPMENT:

Respirators are required for all mixer/loaders.

During airblast application use a closed cab that provides both a physical barrier and respiratory protection (i.e. dust/mist filtering and/or vapour/gas purification system). During application, wear long-sleeved shirt, long pants and chemical-resistant gloves. Keep the following personal protective equipment immediately available for use in case of emergency (i.e. a broken package, spill, or equipment breakdown): chemical-resistant coveralls, chemical-resistant gloves, chemical-resistant headgear and a respirator.

or

If a closed cab is not used, wear long pants, long-sleeved shirt, shoes plus socks, chemical-resistant gloves, chemical-resistant headgear, and chemical-resistant coveralls and NIOSH approved respiratory protection. Chemical-resistant headgear includes So'westers, or large brimmed, waterproof hats and hoods with sufficient neck protection. Avoid touching face or other unprotected parts of the body during application.

Label language should be clarified to indicate directions for water-soluble packaging.

USE PRECAUTIONS:

For commercial orchard use only. Do not use in residential areas such as parks, schools or backyards.

Apply only when the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools and recreational areas is minimal. Take into consideration wind speed, wind direction, temperature, application equipment and sprayer settings.

RESTRICTED ENTRY INTERVAL:

The following restricted entry intervals must be observed by workers re-entering the treated areas for these crops.

Crop	Activity	**REI** (day)
Apples Pears Peaches Nectarines	Thinning	19
	Harvesting, propping, pruning, training	14
	Weeding, irrigating, scouting	12

ENVIRONMENTAL HAZARDS:

- **TOXIC** to aquatic organisms. Observe buffer zones specified under **DIRECTIONS FOR USE**. **TOXIC** to birds
- **TOXIC** to small wild mammals
- **TOXIC** to certain beneficial insects. Minimize spray drift to reduce harmful effects on beneficial insects in habitats next to the application site such as hedgerows and woodland
- To reduce runoff from treated areas into aquatic habitats, consider the characteristics and conditions of the site before treatment. Site characteristics and conditions that may lead to runoff include, but are not limited to: heavy rainfall, moderate to steep slope, bare soil, poorly draining soil (e.g. soils that are compacted or fine textured such as clay).
- Avoid application of this product when heavy rain is forecast.
- Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body.

DIRECTIONS FOR USE

- **DO NOT** apply this product directly to freshwater habitats (such as lakes, rivers, sloughs, ponds, coulees, prairie potholes, creeks, marshes, streams, reservoirs, ditches and wetlands), estuaries or marine habitats.

- **DO NOT** contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.
- **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty.
- **R.E. Airblast or Mist blower application:**
  DO NOT direct spray above plants to be treated. Turn off outward pointing nozzles at row ends and outer rows. **DO NOT** apply when wind speed is greater than 16 km/h at the application site as measured outside of the treatment area on the upwind side.
- **DO NOT** apply this product by air.
- The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands) and estuarine/marine habitats.

Method of application	Crop	Buffer Zones (metres) Required for the Protection of Freshwater Habitat of Depths:	
		Less than 1 m	Greater than 1 m
Airblast (early and late growth stages)	Apple, Pear, Peach, Nectarines	3	1

When a tank mixture is used, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture.